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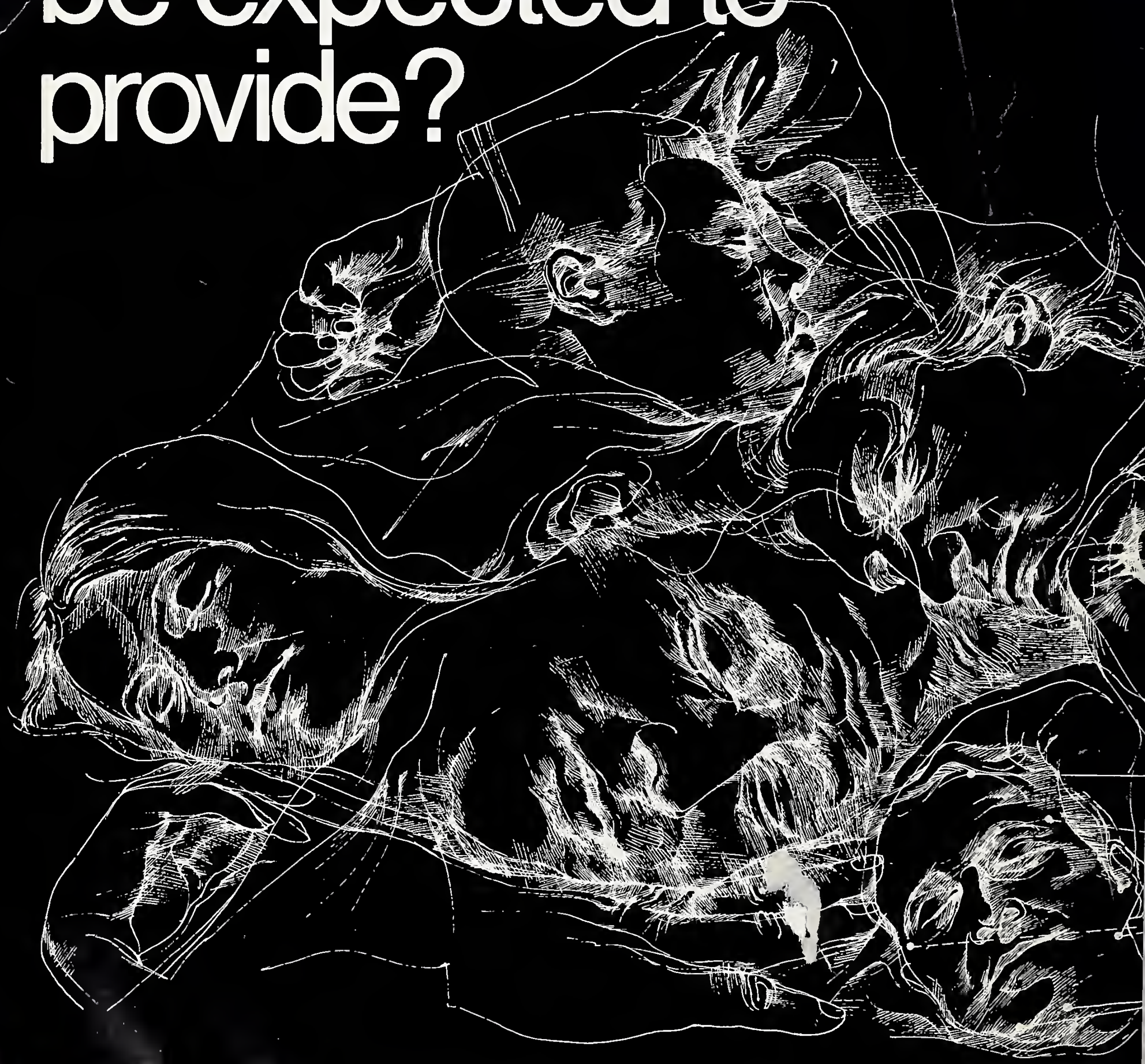

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California Medicine
THE WESTERN JOURNAL OF MEDICINE

Identifying and Counseling Patients with Sickle Trait

W. BYRON SMITH, MD, WILLIAM C. MENTZER, JR., MD, *and* PETER R. DALLMAN, MD
San Francisco

APPROXIMATELY 1,800,000 black people in the United States carry the gene for sickle hemoglobin (Hgb-S).[1] The frequency of the gene and an increased public awareness have stimulated the initiation of sickle screening programs throughout this country.

Among the goals of these programs are: (1) to provide an opportunity for carriers to make informed choices regarding reproduction, (2) to reduce the small risk of vaso-occlusive crises by appropriate advice regarding potentially hazardous environments and occupations, (3) to recognize the homozygotes early in life, and (4) to facilitate identification of sickling variants—many of which have important variations in clinical manifestations. Since sickle trait is so common and relatively benign, with a normal life expectancy, it is essential to avoid arousing inappropriate anxiety in a large number of affected persons and their families. Unless managed skillfully, counseling of one who has this genetic variant has greater potential for harm than good.

As with any large-scale genetic screening program, numerous scientific, social, ethical and legal questions have arisen.[2] The purpose of this presentation is to discuss some of the salient features of screening methods and to provide guidance to the physician who wishes to offer informed counsel to patients with sickle hemoglobinopathies.

Screening Methods

An acceptable screening test for the detection of Hgb-S has several prerequisites: (1) most important, specificity with few or no false positive and false negative results, (2) simplicity so that it can be performed, preferably in a short time, by personnel not having previous laboratory training, and (3) economy. The applicability of various screening tests is summarized in the following section. Causes of false positive and false negative results are given in Table 1; Table 2 lists estimates of relative cost, and Table 3 outlines the type of specimen needed, the time required for performance of the test in the laboratory, and the suitability of the test for the office or field screening.

The moist preparation test, which requires no reagents, is certainly the most easily performed of

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the sickle screening tests.[3] A single drop of blood is placed on a coverslip, inverted on a glass slide, and the edges sealed with vaseline. As the white blood cells consume available oxygen, Hgb-S is de-oxygenated and the red cells sickle. The preparation is examined 24 hours later under a microscope for the presence or absence of sickled cells. Because of the high incidence of false positive and false negative results[3] (Table 1), the length of time required for performance of the test, and the necessity for a microscope to read the result, this test has been supplanted by newer methods.

The (2 percent) sodium metabisulfite ($Na_2S_2O_5$) method has been, until recently, the most popular sickle screening test. One drop of whole blood (oxalated or without anticoagulant) is mixed with a reducing agent (2 percent sodium metabisulfite, prepared fresh daily) to induce sickling, placed on a coverslip, inverted on a glass slide, and examined under a microscope after 30 minutes for the presence or absence of sickled cells.[4] Although false positive and false negative results have been reported[3,4] (Table 1), this test remains an adequate screening device for clinic and office purposes if performed with fresh reagents on fresh whole blood or on blood that had been refrigerated immediately. However, other methods are better suited to mass screening programs.

*Sickledex**,*[5,6] a commercial preparation whose composition is not published, has recently gained recognition as a convenient and reliable screening technique. Twenty microliters of whole blood are collected in ethylenediamine tetraacetic acid

TABLE 1.—*Results of Screening Tests for Hemoglobinopathies*

Test	*False Positive Results*	*False Negative Results*
Moist preparation	1. Coverslip inadequately sealed 2. Too rapid drying	1. Specimen allowed to stand at room temperature too long before placed under coverslip 2. Anticoagulant may inhibit sickling
2% Na-metabisulfite	1. Wrong concentration of Na-metabisulfite (4% may produce sickling with Hgb-AA) 2. Poikilocytes of severe anemia resemble sickled cells 3. Too rapid drying of smear (increases concentration of Na-metabisulfite) 4. Increased humidity in laboratory 5. Pseudo-sickle cells occur as a result of drying at periphery of normal blood smears 6. Presence of Hgb-C$_{\text{Harlem}}$,[81] Hgb-I,[81] and Hgb Barts[82] (which cause sickling)	1. Specimen stored too long at room temperature (temperature and bacterial action alter sickling) 2. Reagent not freshly prepared *daily* 3. Recent transfusion (too little Hgb-S present)
Sickledex	1. Increased globulins, as in myeloma, macroglobulinemia, cryoglobulinemia, and lupus erythematosus[83,84] (increases turbidity) 2. Deterioration of lytic agents (intact red cells increase turbidity) 3. Addition of too much blood to reagent or using blood from polycythemic individual (increases turbidity) 4. Presence of Hgb-C$_{\text{Harlem}}$, Hgb-I and Hgb Barts	1. Inadequate quantity of blood from anemic patients (Hgb <10 gm% and/or Hct <30% (too little Hgb-S present) 2. Deterioration of lytic and/or reducing agents 3. Small concentration of Hgb-S present in the neonate 4. Recent transfusion (too little Hgb-S present) 5. Too bright illumination when reading test 6. Holding tube too close to reading scale
Dithionite tube	1. Essentially the same as for Sickledex 2. Presence of Hgb$_{\text{Alexandra}}$,[7] Hgb$_{\text{Olmstead}}$[85] (which increase turbidity)	1. Essentially the same as for Sickledex 2. Dithionite not prepared fresh *daily* (instability of reducing agent)
Hgb electrophoresis (non-quantitative cellulose acetate)	1. Virtually none if fresh blood (or immediately frozen) utilized; however, does not distinguish other hemoglobins with the mobility of Hgb-S, such as Hgb-D and Hgb-G	1. Detects most known hemoglobinopathies except those migrating as Hgb-A (unstable Hgb, Hgb-M, Hgb with altered O_2 affinity and beta thalassemia minor)

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*Ortho Pharmaceutical Corp., Raritan, N.J.

(EDTA), citrate, oxalate or heparin, and added to 2 ml of buffer solution. After five minutes the test is read macroscopically. The presence of sufficient turbidity to obscure the lines on paper held behind the test tube indicates the presence of sickle hemoglobin. This test depends upon the low solubility of Hgb-S in strong inorganic buffers. False positive and false negative results are uncommon[5] (Table 1). Of particular merit is that blood can be refrigerated one to two weeks before the reagents are added and that the test can be read up to two weeks after the reagents have been added. No microscope or other elaborate equipment is required. The major disadvantage of the Sickledex test, particularly for mass detection, is its high cost (Table 2).

The differential solubility test utilizing sodium dithionite (hydrosulfite) ($Na_2S_2O_4$), proposed by Nalbandian[7] and others,[8] requires that 20 microliters of whole blood in EDTA be added to 2 ml of buffer containing potassium dihydrophosphate, potassium hydrophosphate, sodium dithionite ($Na_2S_2O_4$) and saponin in distilled water. As in the Sickledex test, the presence or absence of turbidity is determined macroscopically after five minutes. The incidence of false positive and false negative results are also similar (Table 1) to those of the Sickledex test. The buffer and saponin stock solution remain stable for three months but fresh dithionite must be added to the amount of stock solution required on the day of the test. Low cost and easy adaptability to automation are cardinal virtues of the dithionite test.

TABLE 2.—*Cost Estimates of Screening Tests for Hemoglobinopathies (Commercial, Private and University Laboratories)**

Test	*Reagents and Supplies (cents)†*	*Technician Time (including collection and processing)‡*	*Total Cost ($)§*
Moist preparation	7.0	2.50	3.57
2% Na-metabisulfite	9.0	3.50	4.59
Sickledex	47.6¶	2.00	3.48
Dithionite	7.0	2.00	3.07
Electrophoresis (non-quantitative cellulose acetate)	5.0	3.50	4.55

*Costs would be considerably reduced in large-volume mass screening programs.
†1969—State of California Relative Value Studies.
‡California Medical Technician salary $5.00 to $5.50/hour.
§Includes estimated overhead of $1.00/test.
¶Based on 100-test kit.

All of the above screening tests fail to distinguish sickle trait from sickle disease and also are inadequate for Hgb-S detection in the newborn. Therefore, hemoglobin electrophoresis should be performed whenever positive results are obtained.

Until recently, *paper or cellulose acetate hemoglobin electrophoresis* has not been available for screening purposes because of expense and the technician time required. Recently, Barnes et al,[9] Petrakis et al,[10] and Kohn [11] have successfully utilized the technique of non-quantitative cellulose acetate electrophoresis for hemoglobin screening. The ability to distinguish Hgb-SS from Hgb-AS is an important advantage. Although Hgb-S can be detected in the newborn, agar gel electrophoresis at pH 6 is required to distinguish sickle disease from sickle trait at this age. A heparinized microcapillary tube filled with whole blood can either be used immediately, stored at 4°C. for several days, or frozen indefinitely. Either whole blood or a hemolysate is applied directly to a cellulose acetate strip, and electrophoresed for 15 minutes. The result can then be evaluated visually. The initial capital outlay for screening equipment can be less than five hundred dollars. False positive and false negative results (Table 1) are unlikely, particularly when fresh specimens are used. Personnel without previous laboratory training can be instructed easily in the use of the electrophoretic apparatus. In addition, many other hemoglobinopathies (but usually not thalassemia trait) can be detected

TABLE 3.—*Requirements and Suitability of Screening Tests for Hemoglobinopathies*

			Suitability for	
Test	*Quantity of blood used for test*	*Time required for lab to obtain result*	*Mass Screening*	*Office or Low Volume Screening*
Moist preparation	1 drop	24 hours	Poor	Poor
2% Na-metabisulfite	1 drop	30 minutes	Fair	Good
Sickledex	20 μl*	5-10 minutes	Excellent	Excellent
Dithionite	20 μl*	5-10 minutes	Excellent	Excellent
Electrophoresis (non-quantitative cellulose acetate)	1-2 heparinized capillary tubes (approximately 75-150 μl)	15-45 minutes	Excellent†	Good

*In patients with Hct <30 percent or Hgb <10 gm per 100 ml, 40 μl of blood must be added to test reagents.
†The only method suitable for screening for Hgb-S in the neonate.

whether they exist independently or in association with Hgb-S. Particularly valuable in this respect is the early identification of Hgb-SC disease which can result in preservation of vision by anticipation and treatment of the characteristic complications of proliferative retinopathy and vitreous hemorrhage.[12,13]

Positive and negative controls ideally should be employed in all of the above-listed screening methods. Since sickle hemoglobin is not commercially available, control blood must be obtained periodically—not an easy task if only sporadic patients are screened as in a private office.

Management of Screening

Population to be screened: Age groups that are particularly suitable for mass screening include the newborn and the adolescent. We favor routine screening of blacks for Hgb-S in the *newborn period,* preferably utilizing cord blood since this involves no trauma. With early identification of the SS homozygote, it may be possible to reduce the high risk of morbidity and mortality that have characterized the disease in infants between six months and three years of age. More, it will provide a record of the majority of persons at risk. This will be of added importance when adequate preventive therapy for vaso-occlusive crises is developed. If screening is postponed until later in the first year of life, many cases may be missed. For example, in a survey of newborns of mothers with sickle and Hgb-C trait, only 45 percent of the children were returned, as requested, to a follow-up clinic at three months of age.[14] However, screening for Hgb-S in the newborn does present special difficulties. Most of the hemoglobin in the newborn period is hemoglobin F.[14] In either the heterozygote or homozygote with hemoglobin S, the small amount of hemoglobin S present at birth is inadequate for reliable detection by screening methods other than electrophoresis (cellulose acetate or paper) of a fresh whole blood specimen. This technique can reveal the presence of hemoglobin S (as small a quantity as 5 percent) but cannot differentiate between sickle trait (AS) and sickle disease (SS) due to poor separation of A and F. Only agar gel electrophoresis at pH 6 will distinguish sickle cell trait from sickle cell disease at birth since it can separate hemoglobin A, S and F. A recent modification of this technique, utilizing a citrate buffer and 3 ml of hemolysate, will allow differentiation of Hgb-S from Hgb-D and distinguish Hgb-C from Hgb-E and O Arab.[14a] If any Hgb-A is present, then the patient cannot be homozygous for Hgb-S.

Recently, mass screening programs have been undertaken in urban high schools by volunteer medical student and public health nursing teams. The target population has been pupils in the 11th and 12th grades. Genetic counseling, to allow informed choices regarding future reproduction, is particularly appropriate in this adolescent age group.

Additional opportunities for screening are presented at the time of induction into the armed forces, during routine antepartum care, and as a part of premarital examinations. Furthermore, all patients admitted to hospital, particularly those requiring anesthesia, should be tested if they do not have results of previous screening available.

The selection of an optimal screening method will depend for the most part upon the health resources of the community. It should be recognized that travel to a screening center is often inconvenient and time-consuming, a factor likely to reduce the effectiveness of a screening program. Thus, in some surveys, few of the persons who are notified that they have sickle trait accept the offer of a counseling session.

Legal considerations. In mass screening programs, non-licensed personnel without previous laboratory experience are commonly utilized. Legal complications can be avoided by careful, although not excessively time-consuming, medical supervision because most tests are easily performed. Positive tests are best verified by a quantitative Hgb electrophoresis and solubility test performed in a licensed laboratory.

Voluntary screening and importance of informed consent. Since the presence of the sickle trait can in no way be considered a public health "menace" and since it is unjustified to project standards of normality based upon an individual's genetic constitution, screening programs should not be compulsory. Although the physical hazards of screening are minimal, some may be concerned about job or insurance discrimination. Signed acknowledgment of informed consent should therefore be obtained regardless of the size of the population being surveyed.

Community involvement. It is appropriate that the Black community be involved in the organization of screening and counseling.[91] Cooperation between medical personnel and the local community is most likely to produce a rational and convenient screening program and avoid the dissemination of alarming information. In addition, the Black community is best equipped to dispose of the issue of genocide raised by some in response to sickle screening programs that project prevention of sickle cell disease as a goal.

Legislation. A bill has recently been passed in the California legislature (Assembly Bill 2786) regarding sickle screening and is being reviewed by the State Board of Health. On admission to a hospital or at the time of the first health evaluation, a person of Afro-American ancestry would be offered a screening test for the presence of sickle hemoglobin.

Background Information

Hgb-S is inherited as an autosomal co-dominant gene. The incidence of this genetic variant in several large groups of Black Americans is 8 to 14 percent for Hgb-AS; 0.3 percent for Hgb-SS; 0.1-0.2 percent for sickle Hgb-C (Hgb-SC); and 0.1 percent for sickle beta thalassemia.[15,16,86]

Sickle trait is a relative benign condition, but there are sporadic reports of a wide variety of untoward results. These are listed here more to provide access to references than for use in counseling. Complications include leg ulcerations,[17] optic atrophy and papilledema,[18] central retinal artery occlusion,[19] progressive retinopathy,[20] hyposthenuria,[21] hematuria,[22-24] renal papillary necrosis,[25] renal failure,[26] renal infarction,[27] an increased incidence of urinary tract infections during pregnancy,[28,29] renal medullary necrosis,[30] splenic,[31-33] cerebral,[34-36] and pulmonary[37-40] infarction; priapism,[41-43] liver infarction and necrosis,[44] increased intrapulmonary shunting,[45] decreased pulmonary function at sea level[46] as measured by decreased steady-state diffusion capacity, anterior and posterior hypopituitarism,[47] spinal cord infarction,[48] mesenteric artery occlusion,[49] jejunal infarction,[50] aseptic necrosis of the femoral heads,[51,52] convulsions and meningeal irritation.[53]

Travel in unpressurized aircraft,[33,39,54-56] exercise at high altitude such as six to eight thousand feet,[56] death following open heart operation,[60] and sudden death during pregnancy[61] have all been associated with vaso-occlusive episodes. General anesthesia has been associated with sudden death and vaso-occlusive episodes in persons with sickle trait;[57-59,87] yet more recent surveys[88-90] have not verified that these patients carry a greater risk than those with normal hemoglobin (AA).

Low birth weight has been reported in babies born to mothers with sickle trait,[62] and a perinatal mortality survey in Ibadan suggested that perinatal deaths were increased in women with sickle trait; however, this work was not confirmed in a recent similar survey in the United States.[63] In the newborn we would not expect symptoms secondary to Hgb-S trait to be produced, even in circumstances of severe hypoxia, because of the very small quantity of Hgb-S present at birth. On the other hand, a death has been reported in a newborn who underwent exchange transfusion with Hgb-AS blood.[64] Experimentally, splenic hypersequestration of red cells in Hgb-AS persons has been induced by exposing volunteers to simulated altitudes of seven to eight thousand feet for 75 to 90 minutes.[65] The abnormal sequestration of red cells tagged with Cr^{51} was first observed one hour after high altitude exposure and was entirely reversed after return to sea level 3 to 5 days later.

In the past, reports of sudden death in patients with Hgb-AS were rare.[36,66-71] Recently, however, four deaths among black males 19 to 21 years of age were reported after brief episodes of unaccustomed vigorous exercise during army combat training at an altitude of 4,062 feet.[72] In each case the pathological changes were consistent with sicklemia in the antemortem period.[70,73] Although the relationship of Hgb-AS to the death of these young men was not entirely clear,[15] it remains possible that under certain environmental conditions the risk for persons with Hgb-AS may be greater than previously suspected.

A person who has sickle trait but no previous symptoms related to the presence of his abnormal hemoglobin is rarely considered an actuarial risk. Our recent survey of 13 life and health insurance companies revealed that 11 of them accept persons with Hgb-AS at usual rates. On the other hand, one company had increased rates for all persons with sickle trait, and another increased rates for those with sickle trait who were less than 20 years of age.

Persons with Hgb-AS are acceptable as blood donors but they should make the blood bank aware of the presence of this genetic trait lest the blood be used in exchange transfusion of a newborn. It is hoped that in the future blood banks will routinely screen for sickle hemoglobin in persons not previously screened. To avoid job and social discrimination, the screening information should be confidential and available only to a designated physician or medical facility.

Counseling

Screening procedures are of little value unless properly followed up with intelligent counseling. It requires judicious counseling to prevent inappropriate anxiety, unnecessary restrictions of lifestyle, and the tendency to attribute all symptoms to the newly-identified sickle trait. As is emphasized by Beutler et al,[74] education of the "at-risk population" and follow-up counseling are just as important as making the test readily available to the public.

Counseling is best done for the individual family although some centers are experimenting with group sessions. The information provided should be kept simple and straightforward, but the counselor should be prepared with a background of more detailed relevant material. Counseling must allay anxiety by reassurance that there is no shortening of life-span associated with sickle trait,[75] that anemia is not caused by sickle trait and that there is minimal likelihood of any future symptoms.[76-79] In the United States, the presence of Hgb-AS appears not to influence either the rate of recognized abortion or maternal fertility.[63,75,80,81] Mention of historical indications that sickle trait may have evolved in some peoples as a protection against malaria may help avoid the stigma often associated with identification of this genetic trait.[76] It is important to emphasize the difference between sickle trait and sickle disease, since this is perhaps the most common source of misunderstanding.

The inheritance pattern and the risks of having a child with either Hgb-AS or sickle cell anemia should be described to individuals and to parents. For example, if two persons with Hgb-AS marry, then with each pregnancy there is a 1:4 chance for an entirely normal child with Hgb-AA, a 1:2 chance for a child with Hgb-AS, and a 1:4 chance for a child with Hgb-SS. If a person with Hgb-SS marries one with Hgb-AS, with each pregnancy there is a 1:2 chance for a child with Hgb-AS and a 1:2 chance for a child with Hgb-SS. Persons with Hgb-AS who marry heterozygotes with Hgb-C or thalassemia will have offspring that may be doubly affected, with syndromes that are generally less severe than Hgb-SS disease. An analogy with coin-tossing can be utilized in demonstrating probability. It is hoped that a description of the clinical course of these diseases will allow parents to make an informed decision regarding family planning. A coloring book* which explains sickle hemoglobinopathies is a useful educational adjunct for both children and parents.

The risks to persons with Hgb-AS all involve unusual *hypoxic situations.* Vigorous, unaccustomed exercise at moderate altitudes (4,000 feet or more) can increase the risk of vaso-occlusive episodes.[72] At high altitudes (more than 6,000 feet), even at rest in an unpressurized aircraft or possibly an automobile, there is an increased risk of a vaso-occlusive episode.[56] Underwater snorkeling or prolonged free-diving also may be hazardous for such persons if hypoxia occurs. These risks are rare and do not deserve undue stress.

All black persons who know they have sickle trait should mention this fact when they are admitted to hospital, particularly if they require anesthesia, whether general or regional. The patient may be provided with a wallet-size identification card containing the results of his quantitative hemoglobin electrophoresis. This will alert his physician to the possibility of unexpected complications in emergency situations.

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Refer to: Brookler MI, Mongan ES: Anserina bursitis—A treatable cause of knee pain in patients with degenerative arthritis. Calif Med 119:8-10, July 1973

Anserina Bursitis

A Treatable Cause of Knee Pain in Patients with Degenerative Arthritis

MORTON I. BROOKLER, MD, *and* EDWARD S. MONGAN, MD, *Downey*

The anserina bursa is located on the medial surface of the tibia deep to the tendons of the sartorius, gracilis, and semimembranosus muscles and superficial to the insertion of the tibial collateral ligament. Knee pain, a palpable swelling of the bursa, and tenderness over the medial anterior aspect of the tibia just below the knee are the hallmarks of anserina bursitis.

In a three-year period, 24 patients with anserina bursitis were seen in a rheumatology clinic. All but one were women, 18 were obese, and only four were under 50 years old. Knee x-ray studies showed degenerative arthritis in 20 of the 24 patients. In ten, varus knee deformities were present, while three had valgus deformities.

Ultrasound or local steroid injections gave dramatic relief in all but one patient.

THE ANSERINA BURSA is located on the medial surface of the tibia deep to the tendons of the sartorious, gracilis, and semimembranosus muscles, and superficial to the insertion of the tibial collateral ligament (Figure 1). In 1937, Moschowitz[1] described anserina bursitis and pointed out that it may simulate chronic arthritis. All his patients were women; they complained of knee pain only on ascending or descending stairs; and on examination, knee flexion or extension was not painful and the joint was not tender. An area of tenderness was found at the insertion of the conjoined tendon of the sartorius, semitendinosus, and gracilis on the inner aspect of the tibia. A slight

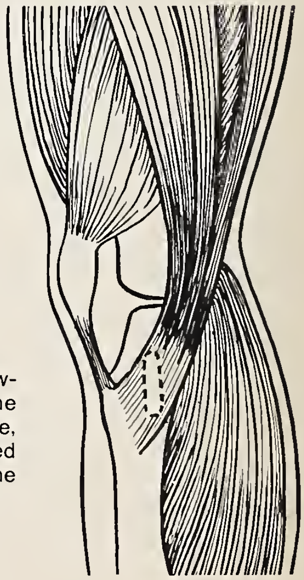

Figure 1.—On this drawing of the muscles on the medial aspect of the knee, the area within the dotted lines is the site of the anserina bursa.

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swelling occurred occasionally in this area. Roentgen examinations were negative. No specific therapy was recommended but Abrams[2] expressed belief that injection of procaine or steroids or both into the tender area may give symptomatic relief.

In a three-year period, 24 patients with anserina bursitis were seen in a rheumatology clinic. The purpose of this paper is to report a correlation between anserina bursitis and degenerative arthritis of the ipsilateral knee, particularly if there is an associated angular deformity.

Methods

All new patients seen in the Rheumatology Clinic at Rancho Los Amigos Hospital and in the office of a rheumatologist in the same geographic area (M.I.B.) from July 1 1969 to June 30 1972 were carefully questioned about pain and examined for swelling or tenderness over the medial aspect of the tibia just distal to the knee—over the area of the anserina bursa. Examination in all cases included a complete history and physical examination, a complete blood cell count, urinalysis, Westergren sedimentation rate, VDRL, antinuclear antiobodies (ANA), and latex fixation tests for rheumatoid arthritis and determination of serum uric acid. Roentgenograms included the chest, hands, wrists, cervical spine, hips, knees, and feet. All films of the knee were weight-bearing films and were read independently by one radiologist who did not know of our interest in anserina bursitis.

Results

Twenty-four patients with anserina bursitis were seen in the three-year period. Table 1 lists the clinical features of these patients. Twenty-three of the patients were women; 18 were obese and all but three were over 45 years old (average age 57.9 years). Fourteen patients had had symptoms in the ipsilateral knee for over one year but none had a history of significant leg trauma. Six of the patients with degenerative knee disease noted a change in the character and intensity of knee pain shortly before presenting with clinical evidence of anserina bursitis. Nine patients had bilateral anserina bursitis. In 20 of the 24 patients, weight-bearing x-ray films of the knees showed degenerative arthritis on the side of the bursitis. In ten patients, varus deformity of the knee was present and three patients had valgus knee deformities. Two patients had rheumatoid arthritis but roentgenograms of their knees showed coexisting changes of degenerative arthritis. All but one of the patients had significant, often a dramatic, relief of symptoms with either ultrasound therapy to the area or injection of adrenocortical steroids into the involved bursa.

Report of a Case

A 66-year-old housewife weighing 236 lb was first seen in the Rheumatology Clinic at Rancho Los Amigos Hospital on February 16 1972. For five years she had noted a dull ache in both knees after prolonged activity. In December 1971 she noted an increase in left knee pain which was aggravated by climbing stairs. On examination, point tenderness and diffuse soft tissue swelling were present on the medial aspect of the left tibia at the site of the anserina bursa. X-ray films of the knee showed changes of degenerative arthritis bilaterally, with some collapse of the medial compartment on the left and a moderate varus deformity. Injection of 0.5 ml of 1 percent Xylocaine® solution plus 2 mg of Decadron® (4 mg per ml) into the swollen left anserina bursa brought pronounced symptomatic improvement within a few minutes. At last report the patient still had

TABLE 1.—*Clinical Data on 24 Patients with Anserina Bursitis*

Sex	*Age*	*Weight (pounds)*	*Changes of Degenerative Arthritis on Knee X-ray Film*	*Anatomical Deformity*
F	71	140	Yes	Valgus
F	31	203	None	None
F	53	214	Yes	Varus
F	68	204	Yes	Varus
F	52	183	Yes	None
F	69	139	Yes	Varus
F	67	192	Yes	Varus
F	55	216	Yes	None
F	52	154	None	None
F	54	136	Yes	Varus
F	68	171	Yes	Valgus
F	70	187	Yes	Varus
F	51	134	Yes	None
F	66	169	Yes	Varus
F	54	166	Yes	None
F	71	195	Yes	None
F	66	236	Yes	Varus
F	54	226	Yes	None
F	23	149	Yes	Valgus
F	56	192	None	None
M	48	165	None	None
F	75	135	Yes	Varus
F	76	199	Yes	Varus
F	40	125	Yes	None

some aching in the left knee after prolonged standing but had not had a recurrence of pain in the left anserina bursa and could climb stairs without difficulty.

Discussion

That repeated minor trauma can cause anserina bursitis is well known to orthopedic surgeons[3,4] and is mentioned by Abrams[2] in the chapter on Traumatic Arthritis and Allied Conditions in Hollander's textbook, *Arthritis and Allied Conditions*. So far as could be determined, this is the first report on an association between degenerative arthritis of the ipsilateral knee and anserina bursitis. Both conditions occur most frequently in obese middle-aged or elderly women. Since knee discomfort in patients with osteoarthritis is usually attributed to the degenerative changes per se, anserina bursitis can be easily missed unless it is specifically looked for. Because ultrasound therapy or injection of adrenocortical steroids into the involved bursa usually give prompt symptomatic relief, it is important not to overlook this easily treated entity.

Anserina bursitis was seen in only two of more than 300 patients with rheumatoid arthritis evaluated during the three years of the study. Both of these patients had a mixed picture of rheumatoid and degenerative change on knee roentgenograms. No anserina bursitis was found in patients with severe roentgenographic changes of rheumatoid arthritis in the knee unless there were coexisting degenerative changes.

It is interesting to speculate that the angular knee deformities present in 13 of the 24 patients put additional stress on the conjoined tendon of the gracilis, sartorius, and semimembranosus muscles, thereby predisposing the patient to anserina bursitis. All cases of angular deformity occurred in the 20 patients with degenerative arthritis of the knee. It appears, therefore, that an obese, older woman with degenerative arthritis of the knees who had had either a recent increase in knee symptoms or who is found to have angular deformity of the knee should be particularly screened for anserina bursitis.

Trade and Generic Names of Drugs

Xylocaine®	lidocaine
Decadron®	dexamethasone

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Refer to: Niswander K: Laminaria tents as an aid in suction abortion. Calif Med 119:11-14, July 1973

Laminaria Tents as an Aid in Suction Abortion

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LAMINARIA HAS PROBABLY been used for centuries to dilate the cervix. The American medical literature of the 1860's and 1870's indicates that laminaria was in common usage in the United States during that period.[1] Infection was a problem that plagued the doctors that used the tents, however, and the tents became a medical relic in the United States, references disappearing from the American medical literature by about 1910.[2] Laminaria tents continued to be used in Europe[3] and their reintroduction in America began two or three years ago. There are already a number of excellent reports of extensive experience with them in the recent American literature.[4-6]

Theoretic uses of laminaria are limited only by one's imagination. Dilatation of the cervix preparatory to invasion of the uterus for intrauterine manipulation is the most obvious use, however. Since gas sterilization has eliminated most of the hazard of infection (Newton reported absence of bacterial growth following gas sterilization even in the middle of the tents), an upsurge of interest in the use of laminaria seems certain.

Laminaria tents are made from laminaria digitata, a species of seaweed which grows in cold ocean waters in various parts of the world. The Japanese have one of the few sources that are both economically accessible and uncontaminated. Seaweed growth in warm ocean waters or plants with hygroscopic action grown on land have historically had a high risk of infection associated with their use and it is probably the relatively clean, cold ocean water that made possible the use of laminaria digitata before adequate gas sterilization became available in the last few years.

The plant, harvested by two-man crews operating from small boats, is brought to shore and placed on drying racks as soon as possible to prevent mold growth from developing. To facilitate drying, the plants are frequently turned on the racks and always positioned so that the stems will dry straight. The dried plants are hand selected and cut to length. Each individual laminaria is shaved to smooth the outer surface.

When packaged, the laminaria tents are about 6 cm long and from 2 to 5 mm in diameter, and they have a string attached to the tip through a hole bored through the tent. Some of the commercially available tents are flared very slightly in their shape so that one end is slightly wider than the other.* Some, however, have an equal diameter throughout.† When placed in water or in tissue the laminaria tent is intensely hygroscopic and swells to three to five times its initial diameter (Figure 1). Most of the swelling apparently takes place in the first six to eight hours, probably less, although it is said that the swelling continues for 24 hours.

Method

This report concerns the use of laminaria tents preceding suction abortion. In the typical case the patient is examined, including pelvic examination, the afternoon before operation. The vagina is cleansed with aqueous zephiran solution. The direction of the cervix is noted and the laminaria tent (typically the medium size) is inserted, usually without difficulty and frequently without the use of a tenaculum on the cervix. In some, but not

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*Milex Products, Inc. (Type B in Figure 1).

†V. Mueller & Co. (Type A in Figure 1).

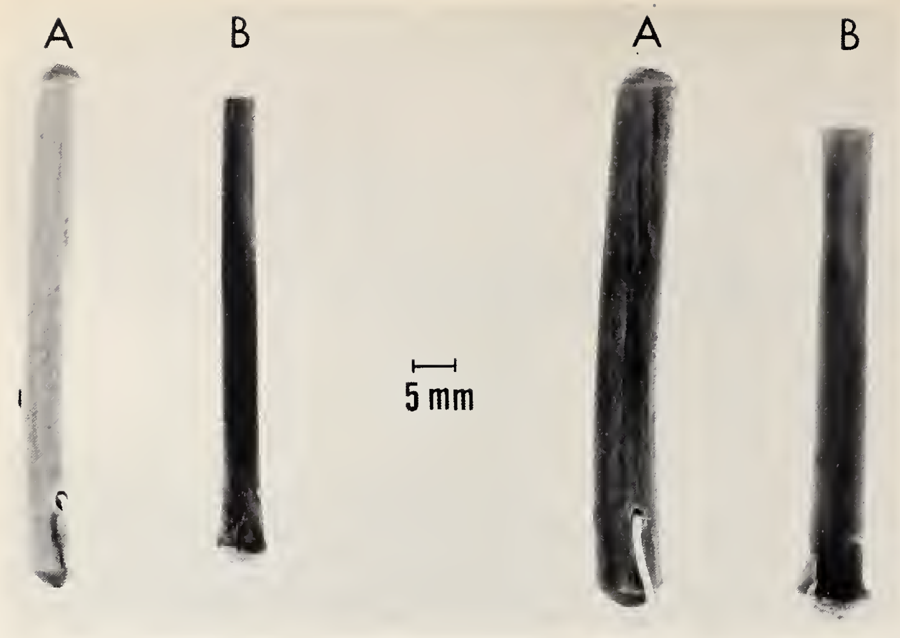

Figure 1.—Two types of laminaria tents. Tent A, V. Mueller. Tent B, Milex. Left—unused. Right, full expansion after placement in water. Note uniform diameter of Tent A and persistence of distal flaring of Tent B.

most, cases the patient has a cramp at the time of insertion. In many patients mild cramps are noted over the next few hours but medication for the cramps is usually not required. (In only one or two instances in our experience was it impossible to insert the laminaria tent, and in three or four cases two tents were inserted into a patulous cervix.)

The following morning the patient is taken to the operating room where the laminaria tent is removed before evacuation of the uterus is begun. No special precautions to prevent infection have been employed. No antibiotic cream is used during the insertion and antibiotics are not given routinely following the abortion.

With appropriate anesthesia the dilatation provided by the laminaria tent is recorded, Hegar dilators being used as the measuring device. Further dilatation, as necessary, is provided with the dilators. Suction curettage is performed in the routine fashion, followed always by brief sharp curettage to insure adequate emptying of the endometrial cavity. Blood and amniotic fluid loss is recorded with precision.

General anesthesia was used in a quarter of our patients, including one patient in whom paracervical anesthesia was insufficient (Table 1). Twenty-seven patients had no anesthesia and the remainder had paracervical block. Preoperative medication for the patients done under local anesthesia usually consisted of morphine sulfate, 10 mg, and diazepam, 5 mg, given subcutaneously about one and a half hours before the procedure. It was unusual for patients under local anesthesia to experience significant pain during the procedure. An occasional patient had severe cramps for a short while after leaving the operating room.

Results

Laminaria tents were used in 327 patients admitted for suction curettage for legal abortion. Fifty-six percent of the patients were nulliparous

TABLE 1.—*Data on Type of Anesthesia and Position of Laminaria at Time of Operation*

	Number	*Percent*
Anesthesia		
Paracervical or none	250	77
General	77	23
Position of Laminaria at Surgery		
In cervix	212	65
In vagina	58	18
Not present	57	17

TABLE 2.—*Data on Parity and Stage of Gestation*

	Number	*Percent*
Parity		
Nulliparous	182	56
Parous	145	44
Gestation		
<8 weeks	41	13
8-10 weeks	177	54
11-12 weeks	91	28
13-14 weeks	15	4
>14 weeks	3	1

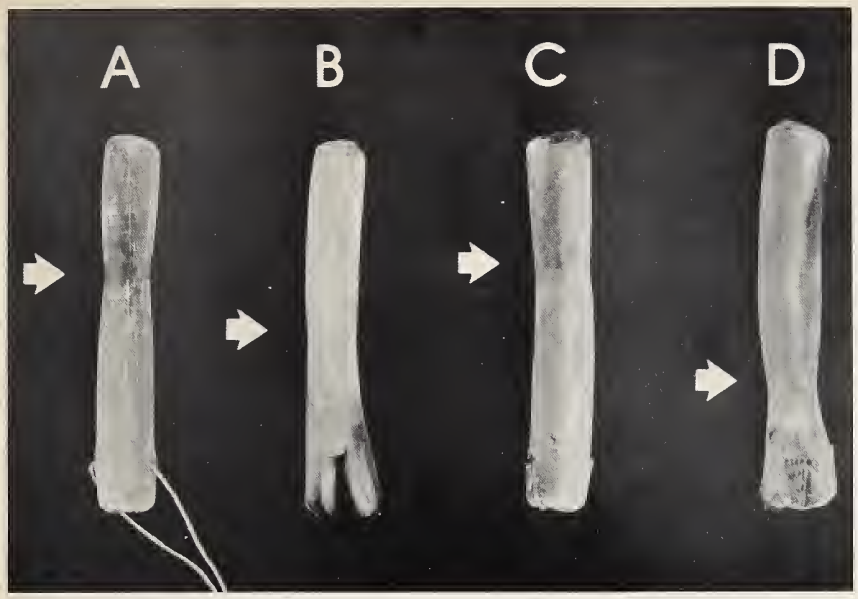

Figure 2.—Type A laminaria tents with uniform diameter throughout from complicated cases. Arrows denote internal os constriction rings. Tent A, normal. Tents B, C, and D identically placed, depict varying degrees of migration, suture pulled out.

and 44 percent were parous; 67 percent were at ten weeks of gestation or less, as estimated by uterine size and confirmed by menstrual dates; 28 percent were at 11 to 12 weeks, and 5 percent were at 13 weeks or more (Table 2).

The position of the laminaria tent was noted at the time of the suction curettage and in two-thirds of the cases it remained in the cervix and was removed therefrom (Table 1). In half of the remaining cases it was lying in the vagina, and in 57 cases it was not found. In most of these cases the patient recalled expelling the laminaria but in a few instances no such history was obtained. In virtually all cases, a thick mucous plug exuded from the cervix.

TABLE 3.—*Cervical Dilatation at Time of Operation*

Weeks of Gestation	*Dilatation (millimeters)* 6 or less	7 to 8	9 to 10	11 or more
10 or less	9%	25%	46%	20%
11 to 12	4%	12%	47%	37%
13 or more	6%	13%	37%	44%

Cervical dilatation measured when the laminaria tent was removed was found to be at least 9 mm in 70 percent of patients (Table 3). Greater dilatation was found more frequently with longer gestational intervals and among parous patients. In 8 percent of patients the dilatation was found to be 6 mm or less—for the most part, fortunately, in patients not long in gestation. Further dilatation to accommodate the needed suction curet was easy in most instances, but in 22 cases some difficulty was encountered with further dilatation.

Not unexpectedly, gestation of greater than 12 weeks was associated with larger blood losses (Table 4). The larger volume of amniotic fluid at later gestations accounts for a small amount of the difference. General anesthesia also increased the blood loss (Table 5). The most important anesthesia difference is with very large blood losses. Only one patient receiving paracervical anesthesia had a blood loss of 500 ml, while five patients under general anesthesia had losses of 1,200, 500, 450, and two of 400 ml.

TABLE 4.—*Blood Loss Related to Duration of Pregnancy (milliliters)*

Weeks of Gestation	*0 to 25*	*<50*	*<100*	*<150*	*<200*	*<250*	*<300*	*>300*
10 or less	12%	43%	33%	6%	5%	..	1%	0.5%
11 to 12	3%	21%	47%	8%	17%	2%	..	1%
13 or more	..	..	17%	22%	17%	11%	5%	28%

TABLE 5.—*Blood Loss Related to Type of Anesthesia (milliliters)*

Anesthesia	*0 to 25*	*<50*	*<100*	*<150*	*<200*	*<250*	*<300*	*>300*
Paracervical and none	12%	34%	40%	5%	7%	1%	0.5%	0.5%
General	4%	24%	38%	13%	10%	2%	4%	6%

Complications occurred with 17 patients. Two had small cervical lacerations from the tenaculum. Tracheotomy was required in three patients, and two of them had postoperative fever. Ten patients had subsequent endometritis or an incomplete abortion and six of these were admitted to hospital for a second dilatation and curettage. None was seriously ill. Two patients had unexplained fever in the postoperative period and one of these probably had an unrecognized perforation of the uterus. She did well after a mild illness of two or three days' duration.

The three patients who required tracheotomy have been described elsewhere.[7] In all three instances, a laminaria tent with uniform diameter throughout its length was used. We now feel that it is important that the distal end of the laminaria be flared slightly to prevent migration of the tent toward the endometrial cavity. Figure 2 illustrates the varying location of the constriction ring produced by the internal os when the tent of uniform diameter is used. Tent A shows what is a usual and normal position of the constriction ring. Tents B, C, and D were placed identically in the cervix at the time of insertion, yet they illustrate varying degrees of migration in the uterus. In all three cases the string of the laminaria tent broke when pulled, and in all three cases the tent migrated so far toward the fundus that it could not be reached with any instrument. Although the surgical procedure required to remove the tent was minor, this certainly must be considered a serious complication.

Discussion

The use of the laminaria tent has greatly simplified our practice of legal abortion. Suction curettage has proved to be easier and safer than sharp curettage[8] but the major problem with abortion has continued to be the difficulty of cervical dilatation. With few exceptions, the use of laminaria tents has eliminated that problem in our practice. It has made possible the use of an outpatient setting for abortion since the pain associated with cervical dilatation is now seldom experienced by our patients. Although we routinely use paracervical anesthesia, it is evident that many of our patients would tolerate the procedure very well without any anesthesia. Paracervical anesthesia without the laminaria tent was found to be inadequate in our hands for instrumental dilatation of the cervix; the use of the tent has changed this situation completely.

Hazards of the laminaria tent should be constantly considered. Certainly our experience and that of Newton et al indicate a low risk of infection with gas-sterilized devices. Perforation with the laminaria tent did not occur in our hands but should be constantly guarded against by gentle and precise sounding of the uterus before insertion of the tent. We have not been able to prevent the occasional premature extrusion of the laminaria tent but this cannot be considered a major hazard. Migration of the tent toward the uterine fundus has not occurred in our experience with an appropriately flared tent. The hazards of legal abortion with the laminaria tent and suction curettage seem greatly reduced as compared with the risk formerly associated with instrumental dilatation and sharp curettage.

We have used laminaria tents before saline solution abortion in an attempt to reduce the time interval between injection and abortion. Our experience is too limited to report at this time. Laminaria tents may be useful in preparing the cervix for an indicated induction of labor near term, and the tents may be helpful in the treatment of cervical strictures, dysmenorrhea, and related conditions.

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Refer to: Meyer GW: Pseudomonas cepacia septicemia associated
with intravenous therapy. Calif Med 119:15-18, July 1973

Pseudomonas Cepacia Septicemia Associated with Intravenous Therapy

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Four cases of Pseudomonas cepacia septicemia were found in one hospital in 1971. Two were related to severe phlebitis of the arms due to intravenous catheters, a third to an infected central venous pressure catheter. The infections resolved after the catheters were removed in these three cases.

Prophylactic antibiotics may play a partial role in predisposing to this kind of infection. Ps. cepacia may be a more common pathogen than previously recognized. Its antibiotic sensitivity pattern distinguishes it from other members of the Pseudomonas family. Nosocomial infection with this bacteria has been traced to quaternary ammonium solutions but the source of infections in the present cases was not found.

RECENTLY TWO PATIENTS RECEIVING intravenous fluid therapy developed septicemia associated with signs and symptoms of systemic disease. Pseudomonas cepacia, sensitive to sulfisoxazole (Gantrisin®), was recovered from each of six blood cultures from one patient and each of three from the other. Review of our laboratory's bacteriology reports for 1971 showed that two other patients receiving intravenous therapy had two or more positive blood cultures for Ps. cepacia.

Reports of Cases

CASE 1. A 24-year-old white woman presented on 25 October 1971 with probable gonococcal arthritis, for which intravenous penicillin was administered. On her third day of treatment her temperature spiked to 39.8°C (103.6°F). Penicillin was discontinued and a new catheter for the fluid therapy was placed in the other arm. On the fourth day use of the catheter was discontinued due to severe phlebitis. During this period six blood cultures were all positive for Ps. cepacia, sensitive only to Gantrisin (see Table 1). After removal of the catheter the patient became afebrile and follow-up blood cultures were negative. The

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Submitted, revised, November 15, 1972. The views expressed herein are those of the author and do not necessarily reflect the views of the U.S. Air Force or the Department of Defense.

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TABLE 1.—*Sensitivity of Pseudomonas Cepacia in Four Cases to Various Antibiotic Agents*

Antibiotic	*Concentration*	*Patient* *Case 1*	*Case 2*	*Case 3*	*Case 4*
Penicillin	10 units	R	R	R	R
Ampicillin	10 μg	R	R	R	R
Cephalothin	10 μg	R	R	R	R
Gentamicin	10 μg	R	R	R	R
Kanamycin	30 μg	R	R	R	R
Tetracycline	30 μg	R	R	R	R
Chloramphenicol	30 μg	R	I	I	S
Streptomycin	10 μg	R	R	R	R
Gantrisin®	300 μg	S	S	S	S
(Colistinsulfate) Coly-Mycin®	10 μg	R	R	R	R
Nitrofurantoin	300 μg	R	R	R	R
Carbenicillin	50 μg	R	R	R	R

R—Resistant; S—Sensitive; I—Incompletely Sensitive

Each strain of Ps. cepacia showed sensitivity to Gantrisin in conventional doses, but showed variable sensitivity to chloramphenicol.

Note: All drugs without ® are generic.

catheter tips were not cultured. No antibiotics other than penicillin were given.

Case 2. A 79-year-old white man had a sigmoid resection for carcinoma on 28 October 1971. The immediate postoperative course was satisfactory until 3 November, when the temperature spiked to 40°C (104°F). No obvious source of infection was identified. Intravenous catheters were changed every other day because of severe bilateral phlebitis in the arms. Each of three blood cultures was positive for Ps. cepacia (sensitivities are shown in Table 1). Intravenous sodium cephalothin (Keflin®), 4 grams a day, had been administered prophylactically from the day of operation. Intravenous penicillin, 20 million units a day, and intramuscular streptomycin, 1 gram a day, were started on 6 November and discontinued on 7 November when intravenous chloramphenicol, 2 grams a day, was started. The patient became disoriented and listless and was considered to be critically ill. The intravenous catheter was removed on 11 November. Within 24 hours he had become afebrile, alert, and hungry. Three follow-up blood cultures, one the evening of 11 November, were negative. Chloramphenical, which had been given orally for four days, was discontinued on 15 November. The patient progressively improved until discharge on 19 November.

Case 3. A 66-year-old white man with severe arteriosclerotic cardiovascular disease and a previous myocardial infarction was readmitted on 15 July 1971 with congestive heart failure. A central venous pressure line (CVP) was placed on 17 July. Daily fever of 38.9°C (102°F) occurred between 20 July and 22 July, followed by two spikes to 40°C (104°F) on 24 July. There was no obvious source of infection found, but two of three cultures of blood drawn in that period were positive for Ps. cepacia (see Table 1 for sensitivities). The central venous pressure line was removed on 24 July and replaced by an intravenous catheter in the arm. Culture of the CVP catheter tip grew Ps. cepacia. The temperature returned to normal over the new few days without administration of antibiotics.

Between 4 August and 12 August the patient was treated successfully with intravenous Keflin for Klebsiella septicemia and he was discharged a week later. No surgical procedures had been performed. Intravenous catheterization was the only invasive technique that had been used when the infection began. There was no record of catheter tip culture.

Case 4. A 45-year-old black woman was readmitted on 9 July 1971 for congestive heart failure and a persistent fever of 38.3°C (101°F) following cholecystectomy in late June. Intravenous Keflin, 8 grams a day, and intramuscular kanamycin, 1 gram a day, were begun for a possible subdiaphragmatic abscess, but the fever continued. Keflin and kanamycin were discontinued on 17 July and intravenous methicillin, 6 grams a day, and intramuscular gentamicin, 120 grams a day, were started. Intravenous penicillin, 20 million units a day, was added on 20 July after the temperature spiked to 41.1°C (106°F) and one observer noted a diastolic murmur. Two blood cultures drawn on 20 July grew Ps. cepacia sensitive to Gantrisin and chloramphenicol (see Table 1). After reexploration on 25 July, each of two blood cultures was positive for Ps. cepacia on 30 July and 2 August, the day the patient died. Autopsy was not permitted.

Investigation of Methods

Choosing the ward from which the most recent infection occurred, cultures were taken from the hands of two nurses and two interns, the arms of three patients, an open tube of polymyxin B-bacitracin-neomycin (Neosporin® ointment) and dry alcohol sponges from the intravenous tray, an open tube of Lubafax and a bottle of green soap found on the ward, the stock supply of benzalkonium chloride (Zephirin®) in the pharmacy, the hospital water, and two unopened bottles of 5 percent dextrose and one-half normal saline solution.

The isolate from one of our patients was reincubated and inoculated into two 125 ml intravenous fluid bottles, one with normal saline solution, the other with 5 percent dextrose in water, to determine whether this species would survive in intravenous fluids.

Blood specimens for cultures are collected by the four laboratory technicians working in the bacteriology department during the day and by two who work nights. They clean the puncture site once from the inside outward with a swab moistened with 70 percent alcohol. Plastic disposable syringes with disposable needles are used. Specimens are transferred aseptically to a bottle with brain heart infusion and to a tube containing thioglycollate broth. After 24 hours, and later if growth occurs, all blood cultures are subcultured on sheep blood agar, chocolate agar and eosin-methylene blue or MacConkey's agar. Organism identification is performed by the "roundtable" method.[1] Antibiotic sensitivity is determined by the Kirby-Bauer disc sensitivity method.[2]

Results

Cultures from the nurses, interns and patients were negative except for an occasional light growth of Staphylococcus epidermidis. The other cultures were sterile. Table 2 shows the growth pattern of Ps. cepacia in the inoculated intravenous fluid bottles over a three-week period. Although there is no reason to suspect bacterial contamination of these bottles (our hospital has used intravenous fluids from the same commercial company for the past six years), it is interesting to note that Ps. cepacia may proliferate in these fluids. At three weeks, however, it apparently outgrew its nutrient supply.

Discussion

Intravenous catheters have long been noted to be a source of possible infection[3,4] and new reports only document infection with additional and normally less pathogenic organisms.[5-7]

Ps. cepacia is an uncommon organism but reports of infection with this bacterium have been increasing. In two cases of endocarditis[8,9] described in 1953 and 1961 the organism was Ps. cepacia.[10] In 1968 Ps. cepacia was isolated from the sputum of a young man with necrotizing pneumonitis.[11] Showing many of the characteristics of melioidosis in this case, the infection was cured by high doses of chloramphenicol, the causative organism being resistant to most other antimicrobial agents. In 1969, an outbreak of urinary tract infection at the University of Minnesota Hospitals led to the discovery that the cleansing germicidal solution in urinary catherization kits was contaminated with Ps. cepacia.[12] The organism disappeared without treatment in eleven of thirteen patients after catheter removal, but two required chloramphenicol therapy to render the urine sterile and the patients asymptomatic. An outbreak of wound infections in another hospital led to the discovery that Ps. cepacia was not only found in the cleansing solution, Savlon®, but also in specimens from the hospital and local water supplies.[13] The cause of three cases of Ps. cepacia septicemia in patients recovering from open heart operations was traced to intra-arterial pressure monitoring equipment which had been cleansed with Detergicide®, a disinfectant containing dimethylbenzylammonium chloride.[14] All three patients were treated for endocarditis because two remained septicemic following removal of intravenous catheters. Another report cited four cases of Ps. cepacia septicemia, three in patients with prosthetic Starr-Edwards valves.[15] In each case the bacteremia persisted after the cannulae had been removed, requiring antibacterial therapy. Unsterilized chlorhexidene solution was found to be the source not only of the infections in these three cases but of positive cultures from a number of wounds and ulcers in other patients and positive urinary cultures in 12 cases.

TABLE 2.—*Growth of Pseudomonas Cepacia in Inoculated Intravenous Fluids*

Time of Incubation	*Concentration per ml in 5 percent dextrose in water*	*Concentration per ml in normal saline solution*
0 hours	..	..
24 hours	$5x10^5$	$5x10^5$
72 hours	$6x10^6$	$2x10^7$
7 days	$5x10^6$	10^8
14 days	$2x10^6$	$6.7x10^7$
21 days	No growth	No growth

The results after inoculation of an incubated strain of Ps. cepacia show it can survive in intravenous fluids for up to three weeks.

Ps. cepacia is a Gram-negative pseudomonad which has also been called Ps. kingii, Ps. multivorans, and EO-1 (Eugonic Oxidiser, Group 1). It is a motile obligate aerobe that oxidatively metabolizes carbohydrate, hydrolyses fat, utilizes citrate, and elaborates catalase. Some strains develop a yellow pigment on triple sugar infusion; others do not. None of the strains reported here produced this pigment.

Ps. cepacia has a unique drug sensitivity pattern, showing resistance to the aminoglycosides but being sensitive to Gantrisin. The strains reported here demonstrated this pattern. Three showed at least intermediate sensitivity to chloramphenicol and all were resistant to carbenicillin. Prophylactic administration of antibiotics did not prevent this infection, nor did seemingly appropriate antibiotics cure it while the catheters remained in place.

Most previous cases of Ps. cepacia infection have been traced to contamination of quaternary ammonium cleansing agents. In the cases reported here the patients were isolated and were housed in different parts of the hospital. The pharmacy reports that such a cleansing agent, Zephiran®, used in this hospital is not used in the wards. When tested the stock of this solution in the pharmacy was found to be sterile.

In reviewing the standard intravenous technique used in this hospital, the only difference from that used elsewhere was that the alcohol swabs used are not the prepackaged commercial kind, but are gauze swabs kept in large containers open to the air, allowing evaporation. A recommendation was made to use the prepackaged kind.

The clinical behavior of Ps. cepacia septicemia was not that of classical Gram-negative septicemia, but was characterized by daily temperature spikes, anorexia, and a general downhill course until appropriate therapy was begun.

It has been suggested that in most cases of infection caused by intravenous catheters, removal of the catheter alone should lead to prompt resolution of fever and toxicity.[4] Two of the four patients herein reported upon had severe phlebitis requiring frequent catheter changes, a third had a CVP catheter contaminated with Ps. cepacia. In Case 1 the temperature and symptoms resolved within 12 hours after removal of the catheter without administration of antibiotics. In Case 3, temperature returned to normal within 72 hours of removal of the CVP line.The Klebsiella septicemia may also have been due to an indwelling catheter, but this was only suggestive. Antibiotics were required for control of the infection. Although the patient in Case 2 received chloramphenicol for seven days, he did not become afebrile or asymptomatic until the day following removal of the intravenous catheter. The death of the patient in Case 4 may have been hastened by the Ps. cepacia but her poor clinical condition before the onset of illness from infection was probably the main cause of death.

Intravenous fluid therapy should include (1) a concerted effort to avoid the use of polyethylene catheters whenever possible, (2) careful aseptic technique in subcutaneous catheter placement equal to that used in surgical cutdowns, (3) the use of antibiotic ointments at the site of insertion, (4) daily dressing change and cleansing of the site, and (5) catheter replacement at least every 48 hours.

The indwelling intravenous catheter should be strongly suspected in patients who have fevers of obscure origin. If continuing intravenous therapy is required, the old catheter should be removed and the tip cultured. A new line should be placed at another site.

ADDENDUM

Since this paper was submitted, Ps. cepacia septicemia developed in another patient receiving intravenous fluids through polyethylene catheters. The infection abated after removal of the catheter. The catheter tip grew Ps. cepacia.

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Medical
PROGRESS

Recent Progress in Epilepsy—
Diagnostic Procedures and Treatment

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EPILEPSY HAS PLAGUED MANKIND for centuries. It was probably first described in ancient Egyptian writings about 2000 B.C. and was a popular topic of the Greek and Roman scholars before the time of Christ.[1] The "falling sickness," as it was frequently called by the ancients, was closely identified with supernatural forces and was considered a manifestation of the gods.

The modern era of epilepsy began with the writings of John Hughlings Jackson in the 1850's. His extensive treatise and the later publications of William Gowers established the neuroanatomical basis for epileptic phenomena, removing them forever from the mystical thinking of the dark ages. The clinical descriptions of seizures by these two physicians were so vivid and complete that observations by present day students of epilepsy have added little.

The introduction of bromides in the late nineteenth century and phenobarbital in the early twentieth century finally afforded the physician a means of treating this disabling disorder. Since the introduction of electroencephalography by Berger in the 1930's, our understanding of the basic neurophysiology of the disease has greatly expanded. Modern research laboratories can now explore function of single neurons residing in an area of experimentally induced epileptic activity and can analyze the data with complex electronic hardware and computers. Today's physician is able to offer his patients sophisticated medical and surgical therapies developed from these diverse experimental models of epilepsy.

Major strides also have been made over the last few decades to increase the public awareness and understanding of epilepsy, yet there still remains much confusion not only among lay persons but in the medical profession as well concerning the role of the epileptic person in society. A review by Boshes in 1965 defined the inequalities in the law when applied to epileptics.[2] Many states still had laws related to eugenic marriages and sterilization that placed the epileptic in the same category as the severely retarded and insane. Two states—Delaware and West Virginia—had laws preventing epileptics from marrying. Even today epileptics have difficulty finding jobs because of persisting superstitions about the illness and, from a more practical standpoint, the employer's inability to obtain adequate industrial insurance. The Federal Immigration Statute existing in 1965[2] excluded epileptics from the United States, along with lepers, paupers and the insane. Recent changes in the immigration laws have rectified this unfortunate situation. Epileptics are required to show proof that they have been seizure-free for one to two years before qualifying for a driver's license, and many cannot find suitable employment unless seizure control is complete and prolonged.

Fortunately, public attitudes toward the disease

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are changing. Caveness et al reported the results of five surveys by the American Institute of Public Opinion spanning the years 1954 to 1969.[3] Representative members of the adult population of the United States were asked questions concerning their knowledge and understanding of epilepsy and their attitudes toward the illness. Persons familiar with epilepsy were asked if they would object if their children played with an epileptic; 57 percent answered "no" in 1954 whereas 81 percent responded similarly in 1969. In 1954, 59 percent stated that epilepsy was not a form of insanity; 81 percent responded similarly in 1969. Twelve percent of persons interviewed in 1969 thought that epileptics should not be employed like other people. Though the trends revealed by this study are encouraging, one is disturbed by the fact that four percent of those interviewed (which extrapolates to an estimated 8,122,000) thought epilepsy was related to insanity.

It is the physician's job, therefore, to educate the public and his colleagues in other professions about epilepsy. He should also expand his own knowledge of the disorder and familiarize himself with the new advances in therapy, thereby affording more epileptics complete seizure control and the opportunity to obtain suitable employment, drivers licenses, and the like.

This review will not cover all facets of epilepsy. It is an attempt to provide a general clinical review of the classification, diagnosis and management of seizure disorders, emphasizing particularly the major advancements in the field over the last few years, such as those in clinical pharmacology. Readers interested in the neurophysiology of epilepsy are referred to several excellent books published within the last few years.[4-6]

Incidence

The prevalence of epilepsy in the general population is usually given as one per 200.[1] This figure varies considerably depending upon the population sampled, the definition of epilepsy and the cause of the seizures. A longitudinal study of 5,000 English children by Cooper[7] revealed an incidence of 22.7 per thousand of one or more seizures among children surviving to the age of two years. The majority of those children having seizures after the age of two had only one or two attacks a year. Kurland[8] studied the incidence and prevalence of seizures in Rochester, Minnesota. His study excluded children with uncomplicated febrile seizures and persons with one convulsive episode, and probably embraced fewer tumor patients than one would expect for a hospital (Mayo Clinic) of that size. The average annual incidence rate (number of new cases per year) age-adjusted to the United States population was about 31 per 100,000 per year. The prevalence rate (number of patients with epilepsy at a specified time) was 376 per 100,000. The incidence rate for primary (idiopathic) grand mal seizures was highest in infants and children and decreased after adolescence; the same was noted for petit mal. Secondary grand mal (cause known) and focal seizures more commonly had their onset at the extremes of age. Birth defects, anoxia, trauma and infection explained the high incidence in children whereas vascular disease and toxic encephalopathy such as alcoholism and tumor were causative in the older age group. Despite minor variations in the actual incidence and prevalence figures from different studies, it is apparent that epilepsy is a major health problem affecting approximately a million persons in this country.

Definition

"Epilepsy" is a term used to define a disorder characterized by recurrent, usually transient episodes of disturbed central nervous system function (seizures) and excludes extracerebral causes such as syncope and episodic psychiatric syndromes. From the physiological viewpoint, a seizure can be defined as an excessive discharge of a population of cortical neurons, the location of the primary discharge and the pattern of spread from the site of initiation determining the seizure's clinical expression. Usually no clinical signs are apparent if the abnormal electrical activity remains confined to a small area of the cortex. The epileptic neurons can be identified interictally* by their propensity to discharge intermittently in synchrony leading to a high-voltage transient event (duration usually less than 100 milliseconds) called a spike or sharp wave. An electroencephalogram using scalp electrodes may record this transient neuronal firing if a significant number of cells are recruited and if the site is close enough to the surface of the brain so that its electrical field will reach the recording electrode on the scalp. In some cases, electrodes must be placed below the surface of the skull (epidural or subdural recording) or actually inserted into the depths of the brain before the focal area of abnormally discharging neurons can be monitored.

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*Between seizures.

The interictal focus may continue its subclinical intermittent paroxysmal activity for periods of time varying from minutes to years and then, for reasons that are not completely understood, the discharge pattern of the "epileptic" neurons changes and the inhibitory systems which have kept the abnormal activity confined to a small area break down. The abnormal electrical activity then spreads to contiguous normal cortex or, by way of anatomical pathways, to other distant neuronal aggregates to which the focus is connected and a seizure occurs (the "ictus"). The spread of epileptic activity through normal cortex can often be appreciated clinically by a chronological history of the sequential phases of the seizure. The patient frequently recognizes a premonitory symptom immediately preceding the ictus which is referred to as an "aura." This word was originally used by Galen (quoted by Lennox[1]) to describe the initial phase of the seizure as "that what rose up was like a cold current of air (aura)." This event actually represents the first portion of the ictus to reach a conscious level and is quite helpful in determining the anatomical site of seizure initiation. For example, an olfactory aura is usually associated with seizures arising from the mesial temporal lobe ("uncinate" seizure), gustatory sensations from lateral frontal (insular) cortex, and crude visual hallucinations from occipital cortex.

Many seizures have a generalized clinical expression associated with the abrupt appearance of a diffuse bilateral and synchronous electroencephalographic pattern. In some cases, close questioning of the patient or witnesses may reveal a brief aura or focal neurological sign immediately preceding the generalized seizure. In other patients, detailed electroencephalographic monitoring of the ictus will reveal subclinical focal seizure activity preceding the diffuse discharge. The diffuse seizure discharge in such cases is thought to arise from the abnormal firing of cells situated in deep subcortical nuclei, such as the thalamus (*vide infra*), that are triggered by the epileptic activity arising in the focus ("secondary bilateral synchrony").

In many patients, however, detailed clinical histories, adequate EEG recordings and the actual witnessing of a seizure by a physician fail to reveal focal characteristics. These generalized seizures, including major motor (grand mal) and petit mal, appear to involve simultaneously widespread areas of the brain. The pathophysiology of this diffuse seizure (electrographically defined as "primary bilateral synchrony") is a controversial issue. The source of these seizures was originally placed in deep subcortical regions by early investigators. Penfield and Jasper referred to this theoretical area as the "centrencephalon" but did not define its exact anatomical boundaries.[4] Since then the term "centrencephalic seizure" has come to define any nonfocal or generalized seizure associated with a diffuse EEG pattern. (Petit mal seizures and the 3-second spike and wave discharge typify the "centrencephalic" seizure). A "centrencephalic" EEG pattern has been produced experimentally by electrical stimulation of the non-specific thalamic nuclei[9] or the mesencephalic reticular formation.[10] Marcus and Watson,[11] on the other hand, demonstrated that a bilaterally synchronous EEG pattern, resembling that of petit mal, resulted from the interaction of two acute cortical foci placed in symmetrical areas of the hemispheres. Mutani et al[12] have described similar diffuse, bilaterally synchronous patterns in cats after chronic epileptic leisons were placed asymmetrically in the two hemispheres. The seizure pattern was not affected by surgically isolating the two hemispheres from the subcortical nuclei, suggesting that cortico-subcortical pathways are not essential for the maintenance of diffuse, bilaterally synchronous electroencephalographic seizure patterns produced by cortical foci. Gloor[13] has developed a theory which, in effect, is a compromise between the purely cortical origin of "centrencephalic" seizures and the subcortical-thalamic or mesencephalic-origin. Through the use of intracarotid amytal studies in man, Gloor concludes that *both* the cortex and the mesodiencephalic reticular formation must participate in these seizures and offers the term "corticoreticular epilepsy" to define the neuroanatomical substrate for the diffuse epilepsies.

It is apparent that the physiological mechanisms and functional anatomy of diffuse seizures are incompletely defined. A vast amount of research has been devoted to the understanding of these seizures but as yet no unified theory has appeared. The reader is referred to several recent publications for more detailed discussions of this controversial seizure pattern.[4,5,14]

Classification

The classification of seizures varies considerably and depends on which aspect of the disorder forms the basis for the classification. Seizures may be categorized solely on the clinical manifestations of

TABLE 1.—*Classification of Seizures**

1. Generalized seizures without focal onset
   - a. Simple absences with impairment of consciousness only
   - b. Complex absences with impairment of consciousness and other phenomena such as automatisms, akinesia or myoclonus
   - c. Bilateral myoclonic jerks
   - d. Infantile spasms (hypsarhythmia)
   - e. Clonic seizures
   - f. Tonic seizures
   - g. Tonic-clonic seizures ("grand mal")
   - h. Akinetic seizures
2. Partial or focal seizures
   - a. Partial seizures with elementary symptoms
     - (1) Motor symptoms
     - (2) Sensory symptoms
   - b. Partial seizures with complex symptoms ("psychomotor" seizures)
     - (1) Automatisms
     - (2) With cognitive symptoms (amnesia *deja vu,* forced thinking, dreamy states, etc.)
     - (3) With affective symptoms (depression, fear, etc.)
     - (4) Psychosensory symptoms (illusions, hallucinations, etc.)
     - (5) Autonomic symptoms (flushing, olfactory sensations, etc.)
3. Partial seizures secondary generalized ("secondary bilateral synchrony")
4. Unilateral seizures—seizures in which the clinical and EEG aspects are analogous to those in group 1e, f, and g except that they are restricted principally, if not exclusively, to one side of the body or one hemisphere respectively (hemitonic, hemiclonic or hemitonic-clonic seizures)
5. Unclassified seizures

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*Adapted from the International Classification of Epilepsy.[15]

the ictal event, on the presumed anatomical or physiological substrate of the seizure, or more simply by etiological criteria—that is, idiopathic or symptomatic. The International League Against Epilepsy has attempted to use all these criteria in developing a standardized and uniform system of grouping seizures. The result of six years of collaboration with many organizations and individuals interested in epilepsy was the extensive classification published in 1970.[15] This classification was recently adopted by the World Health Organization for its Classification of Diseases. Six factors were utilized in the creation of this classification: clinical seizure type, electroencephalographic seizure type, EEG interictal expression, anatomical substrate, etiologic factor, and age of the patient. This classification of seizures (shown in Table 1) represents an adaptation of this international classification.

It is beyond the scope of this paper to discuss each seizure type in detail. Many will be mentioned briefly in other sections of the review concerned with electroencephalography, drug therapy and the prognosis of epilepsy. A brief review of one seizure type—psychomotor seizures (Table 1)—does appear warranted because it represents the most common of the focal seizure disorders, is associated with protean symptomatology and is most amenable to surgical therapy. The febrile seizure of childhood will also be discussed because it represents the most common seizure type of all and the treatment of it is controversial.

Limbic System Seizures

Partial seizures with complex symptoms arise predominantly from epileptogenic foci in the temporal lobes. The characteristic manifestations of seizures arising from this area of the brain were initially described by Hughlings Jackson in 1888.[16] It has been established in subsequent years that purposeful but irrelevant motor activity, hallucinations, illusions, sudden feelings of fear, amnestic episodes, bizarre visceral sensations, distortions of spatial or body percepton and a vast panorama of other psychic or motor activity can occur as a result of seizures arising in the temporal lobe or its immediate anatomical connections which include the limbic system. These seizures have come to be known as temporal lobe, psychomotor or limbic system seizures. The protean clinical expression of psychomotor seizures obligates the physician to investigate thoroughly every patient with recurrent, stereotyped aberrations of behavior that cannot be easily relegated to a specific psychiatric syndrome.

It has been known from the time of Jackson that tumors located in the temporal lobes were associated with psychomotor seizures. The detailed pathological substrate of temporal lobe epilepsy (excluding gross neoplasms) was established conclusively by the examination of tissue surgically removed from patients operated on for intractable epilepsy.[17,18] The most common lesion in temporal lobes removed from intractable epileptics is a characteristic gliosis or scarring termed mesial temporal sclerosis because of its preferential involvement of the hippocampus, amygdaloid nucleus, and uncus. This lesion has been found in aproximately 50 percent of the surgical specimens and is thought to represent an acquired lesion caused by an asphyxial episode in childhood.[19-21] The hypoxic insult affects the hippocampus and amygdala often unilaterally at a time when they are particularly vulnerable, the area of neuronal loss developing into an epileptogenic glial scar years later. Earle et al[19] ascribed the development of this lesion, which they called "incisural sclerosis," to the molding of the skull during delivery, which leads to transtentorial herniation of the brain and compression of the adjacent arteries against the free tentorial edge, with subsequent ischemic infarction of the mesial temporal lobe. Margerison and Corsellis[21] recently questioned the validity of this hypothesis, pointing out that pathological examinations of the entire brain of temporal lobe epileptics frequently reveal the characteristic changes of hypoxia in the cerebral and cerebellar cortices as well as the temporal lobe. Falconer's[20] experience with a large series of surgical patients revealed little historical evidence of significant neonatal asphyxia or trauma. He suggested that severe febrile seizures in infancy may be the acute anoxic insult which leads to the hypoxic damage responsible for the mesial sclerosis. A history of prolonged febrile seizures in childhood was obtained in 40 percent of his patients in whom mesial sclerosis was found at operation. If Falconer's hypothesis is supported by further studies, a more ambitious program for the acute treatment and prophylaxis of "benign" febrile seizures appears to be warranted. The prognosis of febrile seizures is generally reported to be good (3 percent incidence of epilepsy) but most studies have not included patients in the late teens or twenties, the age at which psychomotor seizures frequently appear.

A smaller percentage of temporal lobes removed from patients with refractory psychomotor seizures contain hamartomas, cryptic glial tumors, arteriovenous malformations and post-traumatic lesions. Approximately 20 percent contain nonspecific astrocytic proliferation or lack demonstrable pathology.

Febrile Seizures

Seizures associated with fever in children form the largest single type of convulsive disorder seen by physicians. Approximately 3 percent of children between the ages of six months and five years will experience at least one febrile seizure. The ultimate prognosis is excellent; only 3 percent of children with febrile seizures become epileptic. There are certain general rules followed by pediatricians in their evaluation of the child who has a seizure in the course of a febrile illness. We will discuss some of these general principles in light of a recent prospective report from Denmark where 200 children with febrile seizures were followed clinically and electroencephalographically for at least five years.[22]

1. *Febrile seizures are usually generalized motor seizures, predominantly clonic in type and brief in duration.*—Focal "febrile" seizures are indicative of a local decrease of cortical seizure threshold and, though they may occur in diffuse encephalopathies, should alert the physician to the possibility of a focal destructive process. Contrary to the previously accepted opinion that benign febrile seizures are always generalized, the Danish study reported that 14 percent of the children who were included experienced seizures that were either focal or exceeded 30 minutes in duration and that these seizures carried the same benign prognosis as the more "typical" generalized febrile seizures. We continue to believe, however, that children with such seizures should be evaluated more thoroughly than those with typical febrile seizures. They should be admitted to hospital for observation, and a lumbar puncture, skull x-ray study, electroencephalogram and blood examinations, including serum heterophile titer, should be performed.[23] If seizures recur, fever persists or signs of neurological deterioration appear, the lumbar puncture should be repeated and a brain scan obtained. Arteriography or pneumoencephalography is rarely needed, except in cases where a mass lesion, such as a brain abscess or neoplasm, or herpes simplex encephalitis is suspected. Though we suspect many children with fever and focal seizures have encephalitis despite negative spinal fluid studies, viral serological studies have been generally unrewarding.

2. *Children with febrile seizures have normal electroencephalograms.*—The EEGs of most children with febrile seizures do not contain paroxysmal or epileptiform abnormalities but many will be abnormal if obtained within a week to ten days after the seizure. The most common abnormality is excessive slowing, usually expressed maximally in the occipital areas and occasionally quite asymmetrically. About one-third of the initial EEGs in the Danish study revealed such slowing, but more importantly, this abnormality carried no prognostic implications.[22]

One of the major contributions of the Danish study concerned the incidence of EEG abnormalities on subsequent examinations obtained when the child was well. In approximately 30 percent paroxysmal EEG abnormalities developed at an older age. Nineteen of these children had focal spike discharges on subsequent records. The authors attempted to correlate this surprisingly high incidence of asymptomatic epileptiform EEG activity with the well-known fact that a family history of seizures exists in a high proportion of children with febrile seizures (about 40 percent).

Since seizure threshold appears to be genetically determined, a person with a genetically low threshold will more readily have seizures regardless of cause. If one examines a group of patients with head trauma of similar severity, those with a family history of seizures will have a greater chance of developing post-traumatic epilepsy than patients with identical brain lesions but no family history of seizures.[24]

Children with benign febrile seizures, therefore, may represent that segment of the population with genetically determined low seizure thresholds. The fever lowers the threshold to the critical point by mechanisms not understood and a seizure occurs. The EEG abnormalities noted later in life may represent further evidence of this lowered threshold, which may never again reach the point where clinical seizures appear.

It is well known that a small percentage of normal children have abnormal EEGS, occasionally manifested by epileptiform activity. The physician should weigh carefully the correlation between such unexpected EEG findings and the patient's clinical complaints, particularly if they consist of symptoms such as headache, behavioral disturbances, school phobias and the like. A strong family history of febrile seizures may suggest the mechanism for the EEG findings.

3. *Benign febrile seizures never begin after age five.*—Febrile seizures appearing initially at an earlier age, rarely recur after age five. Any child with the onset of seizures after the age of five years, despite the presence of a fever, should be considered to have a symptomatic seizure disorder and the appropriate diagnostic evaluation immediately initiated.

4. *Treatment of febrile seizures.*—Most pediatricians rely on two therapeutic regimens to prevent further febrile seizures. The child is either placed on chronic phenobarbital or diphenylhydantoin (DPH) or given prophylactic phenobarbital with the onset of a febrile illness. The latter approach is impractical because there will be a delay between the initiation of therapy and the establishment of therapeutic blood levels. High oral doses (three or four times the usual maintenance dose) would be needed if therapeutic levels are to be reached within the first 24 hours following beginning of therapy. Furthermore, the temperature elevation is often discovered only after the seizure has occurred. Maintenance therapy with DPH or phenobarbital has also been advocated, but most parents are reluctant or unable to administer daily medication to an otherwise healthy child. A recent prospective study of the use of DPH prophylactically showed it to be ineffective in preventing febrile convulsions in children under three years of age.[25] Another study from the same group, however, indicated that daily oral phenobarbital significantly reduced the incidence of recurrent febrile seizures if the serum phenobarbital level was maintained above 1.5 mg per 100 ml.[26] Febrile seizures recurred in 21 percent of children with phenobarbital levels below 1.5 mg per 100 ml, whereas only 4 percent of those with levels above 1.5 mg had recurrences. In a previous study, the six-month recurrence rate in 176 untreated children under three years of age was 20 percent.[27]

The incidence of recurrence of febrile seizures is most closely correlated with the age of the child at the time of the first seizure.[22] If the first seizure occurs under the age of 13 months, there is a 66 percent incidence of recurrence compared with recurrence rates of 50 percent and 20 percent respectively for children having their first seizure at 14 to 32 months and more than 32 months. Therefore, prophylactic oral phenobarbital, given twice daily, is probably indicated in the younger child with the greater chance of recurrence. Serum phenobarbital levels should be determined at random times and the parents instructed in the reasons for maintaining chronic therapy.

Value of the Electroencephalogram

The diagnosis of epilepsy is primarily a clinical rather than an electroencephalographic process. However, in many instances the EEG will yield unique information critical to the evaluation of the epileptic patient. If the physician is to use this laboratory procedure properly, he should be familiar with the basic principles of electroencephalography, particularly those related to the preparation of the patient for the test and the maneuvers available during the test that increase the chance of recording abnormal electrical activity.

There are relatively few EEG abnormalities that are pathognomonic for a specific neurological disease. Some epileptiform potentials, however, may be correlated with specific seizure syndromes—for example the 3 per second wave and spike complex with petit mal seizures. Children thought to have petit mal seizures should always be hyperventilated and exposed to intermittent photic stimulation during the EEG recording because a clinical and electrographic seizure may be precipitated. (Hyperventilation for three minutes is also a useful office procedure if the physician wants to witness an actual seizure.)

The EEG may not only be useful in diagnosing petit mal seizures but also in predicting the clinical outcome of children with this rather rare seizure type (less than 5 percent of children attending epileptic clinics are found to have petit mal[28]). The seizure disorder should only be classified as petit mal if the child has brief absence episodes and the EEG reveals the typical epileptiform pattern. The EEGs of virtually all children with petit mal epilepsy contain 3 per second spike and slow wave discharges in either the awake resting tracing, during hyperventilation, photic stimulation or, rarely, only in the tracing obtained asleep.[29] Most of the children referred to our clinic with the diagnosis of petit mal seizures are found to have other varieties of epilepsy, particularly psychomotor seizures, photic sensitive seizures, myoclonic epilepsy and the absence attacks associated with petit mal variant patterns on the EEG (*vide infra*). In Gibberd's study of 139 patients, the EEG findings did not influence the prognosis for petit mal seizures.[30] However, there was a strong association between an abnormal background activity on the EEG (the cerebral electrical activity other than the paroxysmal events) and the occurrence of grand mal seizures. In 40 percent of the children with normal background rhythms grand mal seizures ultimately developed, compared with 77 percent of those with abnormal background. (Petit mal, therefore, is not a benign seizure disorder that most children will "outgrow.")

Petit mal variant (Lennox-Gastaut syndrome, childhood epileptic encephalopathy with slow spike-wave) is an electroencephalographic and clinical syndrome seen in children with a variety of seizure types. The EEG discharges consist of spike and slow wave activity at less than 3 per second and are often associated with diffuse disturbances of background rhythms. This heterogeneous group of children are often retarded; have a variety of tonic, tonic-clonic, absence or myoclonic attacks; and are notoriously difficult to control with drugs.[31] They should not be confused with children having petit mal seizures because their prognosis for normal intellectual and neurological development is poor.

If focal electroencephalographic abnormalities are seen in epileptic patients with generalized seizures and normal results of neurological examination, the physician should consider the possibility of a focal destructive process, such as a neoplasm, arteriovenous malformation, cicatrix or, in older patients, an area of cerebral ischemia secondary to a vascular occlusion. The appearance of a temporal lobe spike in a patient with episodes of disturbed behavior may be critical evidence of an organic basis for the attacks.

An abnormal electroencephalographic response to intermittent photic stimulation ("photoconvulsive response") suggests a diffuse abnormality of the cerebral neurons and is evidence against a focal process. (Photic stimulation rarely activates focal seizures, even those arising in the occipital lobe.) A photoconvulsive response suggests a hereditary or idiopathic seizure disorder, particularly in younger patients with epilepsy. We have frequently found abnormal photic responses in the EEGs of the asymptomatic siblings of epileptic children with photoconvulsive responses, confirming the familial nature of the process. A similar response may also be seen in barbiturate or alcohol withdrawal, certain metabolic encephalopathies, particularly uremia, and in the rare degenerative or neuronal storage diseases, but these will be associated with other clinical findings. Occasionally, photoconvulsive responses are obtained in the EEGs of adults with generalized seizures of recent onset who ultimately admit to the recent ingestion of illicit barbiturates; the EEG in these instances has fortuitously been obtained during a withdrawal state. A random screening of the urine for drugs may be indicated, therefore, in adolescents and young adults with photoconvulsive responses despite a negative history of drug ingestion. A photoconvulsive response may also be found in a small proportion (approximately 3 percent) of the normal population.[32]

The physician might consider obtaining EEGs on the relatives of seizure patients when the cause of the seizures is in doubt. For example, in certain medical-legal situations, seizures may be attributed to preceding trauma. The finding of similar epileptiform abnormalities in siblings or near relatives would suggest a familial seizure disorder with clinical expression in the proband only. It is also unlikely that such a patient would be harboring a tumor, unless one is dealing with neurofibromatosis, tuberous sclerosis or one of the other rare hereditary neurocutaneous syndromes characterized by cerebral neoplasia and epilepsy.

Focal epileptiform abnormalities in the EEG are usually associated with a focal destructive or "irritative" lesion. In children, however, focal spikes in the central or temporal scalp areas may carry the same familial connotation as the 3 per second spike and slow wave of petit mal. Bray and Wiser[33] have recently described a group of epileptic children, selected because their EEGs demonstrated a focal epileptiform discharge in the temporal or central areas, in which 36 percent of close relatives demonstrated similar focal or, in some cases, diffuse discharges. Their family studies suggested a dominant pattern of inheritance with age dependent penetrance (peak clinical expression in middle childhood). They noted that the EEGs of many of the clinically unaffected relatives contained diffuse symmetrical paroxysmal activity, the type more classically associated with familial seizure disorders such as petit mal.

The EEG may reveal other abnormalities of cerebral electrical activity (in addition to purely epileptiform activity) which aid the clinician's evaluation of the patient. Focal slowing and attenuation of normal background rhythms may suggest a destructive process, particularly if previous EEGs were normal or merely showed epileptiform activity. One must be cautious in interpreting such activity, however, if the patient has had a seizure during the several days preceding the record. Severe or prolonged motor or sensory, psychomotor or generalized motor seizures are more apt to produce postictal EEG slowing than are minor episodes, whereas petit mal seizures are not associated with such persisting EEG abnormalities. The temporal relationship of the patient's last seizure and the EEG, therefore, should be determined before one can conclude that the EEG represents a deterioration from previous records. (Further discussion of the EEG in epilepsy can be found in the section on status epilepticus.)

A normal electroencephalogram may be found in a high proportion of epileptic patients depending, in part, upon the thoroughness and frequency of the examinations. Ajmone Marsan and Zivin,[34] in a recent review analyzing the various factors which might influence the presence or absence of typical epileptiform discharges in the EEG, found that only 56 percent of epileptic patients had epileptiform patterns on their initial EEG. (A higher proportion, of course, will have non-epileptiform abnormalities such as diffuse slowing.) They found that certain factors significantly influenced the effectiveness of the EEG in confirming the clinical diagnosis.

1. *Age of the patient.*—The percentage of patients with positive tracings (that is, with epileptiform patterns) progressively decreased with age with negative tracings predominating above age 40. Patients whose seizures began at a later age also tended to have more normal or non-specifically abnormal EEGs.

2. *Abnormal EEGs are more apt to occur if the patient had a seizure within the few days preceding the recording.*—Patients with more frequent seizures tended to have a higher incidence of positive EEGs.

The etiology of the seizure disorder, type of seizures (except for psychomotor seizures and petit mal), and medication did not appear to influence the EEG results. The latter finding is of practical importance because of the common practice in some laboratories to discontinue anticonvulsant drugs before the EEG examination is carried out. The half-life of most anticonvulsants is so long that serum levels are not significantly lowered by discontinuing drugs 24 hours before the tracing. Of more importance, Ajmone Marsan and Zivin[34] concluded that patients consuming anticonvulsants did not have a higher proportion of normal tracings. It is the practice of our laboratory not to alter the patient's drug regimen before the EEG. (The suppression of petit mal seizures with the succinamides or diones is the major exception to this general rule.) Only in the case of patients with questionable seizure disorders and negative serial EEGs should anticonvulsants be withdrawn, usually under hospital supervision.

How can the physician, therefore, increase the yield of abnormal EEGs in patients with suspected seizure disorders? If one considers the natural history and type of seizure and the technical capabilities of the EEG laboratory, a more intelligent use of electroencephalography can be made.

1. Obtain the EEG at a time when the patient historically has the highest seizure frequency—for example, children with myoclonic seizures may note a concentration of seizures in the early morning, some women have more seizures about the menstrual periods, some patients may note an increased seizure frequency later in the day when fatigued, and the like.

2. Always obtain an electroencephalogram with the patient awake and asleep. It is well known that many epileptiform abnormalities, particularly those located in the temporal lobe, will be seen only when the patient is falling asleep or is lightly asleep.[35] Sedation may be needed and will not contaminate the tracing. (We prefer oral chloral hydrate in our laboratory because it does not produce the fast cerebral activity characteristic of the barbiturates.) If an abnormality is noted in the tracing with the patient awake, a tracing during sleep is still indicated. If the waking EEG reveals an unilateral epileptiform abnormality in the temporal region, a tumor may be suspected. If an independent spike appears in the contralateral temporal region with the patient asleep, the chances of a tumor are significantly reduced. Further, the focal nature of the epileptiform abnormality may only be appreciated in the sleep tracing, as an awake record may reveal only diffuse paroxysmal activity.

3. Sleep deprivation has become a frequent activating procedure in many laboratories. It is well known that many epileptics note an increase in seizure frequency following sleep loss. Studies of prolonged sleep deprivation in normal persons have also revealed epileptiform patterns in some of them and, less frequently, clinical seizures were precipitated. In one study, 34 percent of a group of epileptic patients with previously normal EEGs had epileptiform patterns on tracings obtained after a single night's sleep deprivation.[36] It is routine in our laboratory to instruct patients, including children, to remain awake the night before the EEG, particularly if the patient is being referred from such a distance that serial tracings may be impracticable or if previous EEGs were normal.

4. Nasopharyngeal (NP) electrodes should be utilized in all adolescent or adult patients with seizures, particularly if there is a clinical suspicion that the seizures arise from the temporal lobes or if previous EEGs have been normal or revealed only diffuse abnormalities. They are indicated in the evaluation of patients with periodic behavior syndromes, episodes of loss of consciousness of unknown cause or periodic or recurrent sleep disorders. The NP electrode consists of a pliable nontraumatic coated wire which is inserted through each nostril and comes to rest against the superolateral wall of the nasopharynx. It records the electrical activity of the inferomesial portion of the temporal lobe, an area from which seizures frequently arise and which is not accessible to the routinely applied scalp electrodes. After minimal training, the electroencephalographic technologist can easily insert these electrodes without direct physician supervision. It is the policy of our laboratory for the technologist to insert these electrodes, when indicated in all patients with seizures without a direct order from the physician. After insertion of the electrodes, the patient should be allowed to sleep (with sedation, if needed). Many of the epileptiform potentials arising from the mesial temporal area appear only during light stages of sleep or in the transition from wakefulness to sleep. We have recorded epileptiform activity confined to these electrodes on enough occasions to feel justified in using them routinely. de Jesus and Masland demonstrated that 17.5 percent of their patients with satisfactory sleep and NP tracings had significant electroencephalographic abnormalities confined to the NP leads.[37]

5. All patients should be hyperventilated for 3 minutes unless it is clinically contraindicated because of recent cardiac, pulmonary or cerebral vascular disease. Photic stimulation, as mentioned above, is also a useful activating procedure in all patients with possible seizure disorders. If this procedure is to be used efficiently, a variety of stimulus frequencies should be presented to the patient with his eyes open and closed. The patient should be awake when photically stimulated, because a photoconvulsive response may disappear in light sleep.[38] This fact is often overlooked in children, the technologist preferring to keep the child asleep to avoid movement artifact.

6. It has been suggested that intravenous or intramuscular methohexital (Brevital®) given during or preceding the EEG is a potent activating agent and may be useful in evaluating patients suspected of seizure disorders.[39,40] This drug must be used with caution, however, because respiratory depression occurs with dosages just above those recommended for activation. Celesia and Paulsen[41] failed to confirm these earlier reports and found that an adequate sleep tracing was as effective in activating paroxysmal abnormalities as intravenous methohexital. Further controlled studies are required before this drug can be recommended for routine laboratory use.

7. The patient should be questioned closely about the circumstances preceding the seizure. An occasional patient will note that certain sensory stimuli, such as sound (often in a very specific

form, such as a certain song or a certain person's voice) or touching a certain part of the body, or a particular body movement, or even a passage of reading, will precipitate a seizure. Some patients may produce a seizure at will by concentrating on a particular scene or event. Such types of reflex epilepsy are rare, but the precipitating circumstances should be reproduced during the EEG recording.

A negative EEG, despite these maneuvers, should not be taken as evidence against a seizure disorder. Often repeated tracings are needed before epileptiform activity is finally recorded. In Ajmone Marsan and Zivin's series, approximately 8 percent of 75 patients who were followed with repeated examination for at least one year had persistently negative tracings.[34] On the other hand, an EEG containing epileptiform activity does not necessarily classify the patient as epileptic. The EEG must be correlated with the clinical situation, and the final decision concerning the cause of the patient's complaints rests with the clinician.

The all-too-common practice of "treating the EEG" should be abandoned. Rarely should the dose of anticonvulsant drugs be increased, solely on the basis of persisting paroxysmal activity on a follow-up EEG, in a patient whose seizures are well controlled. Serial EEGs are useful in the early stages of therapy as corroborative evidence that the seizures are waning. They are also useful as a periodic screening procedure in patients suspected of harboring a neoplasm, in those with changing seizure patterns, or in those in whom drug control breaks down.

When to Discontinue Anticonvulsants

The EEG has been proposed as a useful adjunct in deciding if anticonvulsants should be discontinued in patients whose seizures have been controlled for many years. This is a frequent and usually difficult decision for the physician who must weigh many factors before agreeing to the patient's request to discontinue drugs. The major problems involved are the frequency of seizure recurrence after withdrawal and the toxic effects of the anticonvulsant drugs. Juul-Jansen[42] studied the various factors which appear to influence the recurrence of seizures in 200 patients withdrawn from drugs after freedom from seizures for at least two years. He excluded patients with progressive brain disease, those with progressively abnormal EEGs, children approaching puberty and patients in whom recurrence would result in social difficulties. He concluded that the following factors were associated with an unfavorable prognosis, that is, were more often associated with seizure recurrence:

1. There was a higher recurrence rate in patients whose seizures were graded as severe before the institution of therapy (as compared with patients experiencing only a few seizures before control).
2. Recurrences were more common in patients whose seizures began after the age of 30 (52 percent versus 30 percent for those below 30 years).
3. If the EEG obtained at the time therapy was begun or just before withdrawal of drugs contained focal slowing or bilateral paroxysmal activity (not defined by Juul-Jansen), the recurrence rate was higher.

The recurrence rate was not adversely affected by the presence of spike foci in the EEG obtained before the beginning of therapy. The good prognosis of epileptic children whose EEGs reveal occipital or centrotemporal spike foci may have accounted for this finding.[33,43,44] The type of epilepsy, pathogenesis of the seizures, degree of cortical atrophy indicated by pneumoencephalography and the age of the patient at the time of withdrawal were not important.

A five-year followup of these patients was recently presented by Juul-Jensen.[45] Seizures had recurred in 40 percent, 44 percent of the recurrences occurring in close relation to the discontinuance of medication and 73 percent of the recurrences appearing within the first year after drug withdrawal.

The importance of the EEG has recently been questioned by Holowach et al[46] in a study of seizure recurrence in children withdrawn from anticonvulsant drugs following a four-year period of seizure control. They stated that the EEG obtained immediately before discontinuance of drugs was of little value in predicting recurrence. Their figures, however, do not entirely agree with this statement. Sixteen percent of children with normal tracings had relapses, whereas in the children whose EEGs revealed mild, moderate and severe paroxysmal disturbances, recurrence rates of 29 percent, 24 percent and 50 percent, respectively, were obtained. Unfortunately, no statistical analysis of the data was performed and the criteria for EEG classification were not presented. The overall relapse rate in their series, excluding uncomplicated febrile seizures, was 28 percent. Children whose seizures began early in life and were quickly controlled had a better prognosis than those whose seizures began in infancy or later in life and were initially resistant to therapy. Patients who had generalized motor seizures ("grand mal type") before control had a lower recurrence rate after drug withdrawal (8 percent) than those with Jacksonian (53 percent), psychomotor (25 percent), or combinations of seizures (40 percent).

It is our feeling that electroencephalograms should be obtained before drug withdrawal in all patients. If epileptiform abnormalities persist, drug withdrawal is usually postponed or the patient is informed that the recurrence risk may be higher. Drugs are gradually withdrawn over a period of several months and EEGs are obtained periodically. If epileptiform abnormalities appear or there is a deterioration of previous abnormalities, drug withdrawal is discontinued. It is common practice to avoid drug withdrawal in children until they pass puberty. Holowach et al[46] did not find that the recurrence rate was higher in children from whom drugs were withdrawn during this period and suggested that discontinuance of drugs need not be postponed because the child is approaching puberty.

One should also discuss with the patient the possible adverse consequences of withdrawal, such as the influence on job, school performance, and driving privileges. Patients are encouraged not to drive during the withdrawal period and for several months thereafter. Withdrawal in school-age patients is started just before completion of a school year; then if seizures are to recur they probably will happen during the summer vacation when the social embarrassment still (regrettably) associated with epilepsy would be at a minimum. There is no evidence that seizures are more difficult to control after a recurrence, and reinstitution of the previous anticonvulsants usually provides complete seizure control.

Brain Tumor and Epilepsy

Epileptic patients are frequently referred to our clinic because their physician is concerned about the possibility of an underlying cerebral neoplasm. In our experience the following factors should be considered when evaluating such patients:

Age of the patient.—Brain tumors associated with seizures usually involve the cortex of the cerebral hemispheres. Seizures are rare with deep tumors, such as those involving the thalamus, and occur with posterior fossa lesions only when increased intracranial pressure or metastatic spread is present. Approximately two-thirds of cerebral neoplasms in children are located in the posterior fossa and of the remaining one-third, approximately one-half occur near the midline—pituitary tumors, for example. It is unwarranted, therefore, to evaluate every child with seizures for neoplasia. An electroencephalogram and skull x-ray study are obtained on all children with seizures, but brain scans and contrast studies are not performed unless a progressive neurological syndrome is present. A lumbar puncture should be performed on most children after their first seizure, particularly if infection or subarachnoid hemorrhage is suspected. A significant elevation of the spinal fluid protein may suggest a progressive degenerative or storage disease, a mass lesion or other destructive process. It should be emphasized, however, that seizures are not uncommon in children with brain tumors. Backus and Millichap found that seizures occurred in 17 percent of 291 children treated for intracranial tumor at the Mayo Clinic.[47]

The incidence of tumors in patients with adult-onset seizures is about 10 or 15 percent, though the relative frequency varies according to the bias of the study. Martin and McDowell found mass lesions in 38 of 106 patients with generalized seizures beginning after the age of 35 (as compared with 12 of 84 patients under age age of 35).[48] Of 34 patients with focal seizures starting after the age of 35, 24 had mass lesions (as compared with 9 of 21 patients under 35). Ang and Utterback, on the other hand, found tumors in only 4 percent of their 96 patients over 40 years of age, whereas "vascular" disease was causative in 48 percent.[49] White, Bailey and Bickford found the incidence of tumor to be 11 percent in their patients over 50 years.[50] Juul-Jensen diagnosed tumor in 3.7 percent of his series of 1,020 adult patients.[51] This increased to 15 percent in patients with the onset of seizures beyond the age of 50. (The seizures in 69 percent of these older patients were attributed to cerebrovascular disease.) Sumi and Teasdall's evaluation of patients with focal seizures (exclusive of psychomotor and adverse seizures) revealed a 35 percent incidence of tumor.[52] Falconer et al found cryptic tumors (usually hamartomas or low grade gliomas) in 23 percent of their patients undergoing temporal lobectomy for refractory seizures.[18]

Neurological examination.—Adult patients with seizures and focal abnormalities on neurological examination, particularly if the abnormalities are progressive, should be evaluated for neoplasm unless the history of a significant neurological insult such as trauma or meningitis can be obtained. All patients with adult-onset seizures, unless the cause is obvious, should have a brain scan (with delayed views)[53] and a cerebral blood flow study regardless of the status of the neurological examination. All adult patients, even if seizures are well controlled, should have periodic examinations and EEGS. Patients with temporal lobe seizures should have periodic visual field studies. Tumors in this region may spread into the posterior temporal lobe and involve the optic radiation before more obvious motor or sensory impairment appears. All adults, particularly those with focal or progressive seizure disorders, should be thoroughly screened for an occult malignant disease. In the initial evaluation of a patient with adult-onset seizures the examination should include a thorough search for adenopathy, skin lesions, organomegaly, breast masses and the like. Blood studies should include liver function tests and determination of serum calcium. A complete blood cell count, urinalysis and stool guaiac test are mandatory. A chest x-ray study should be obtained because of the high incidence of cerebral metastasis from carcinoma of the lung.

Unexplained increases in seizure frequency, recurrence of seizures after long periods of control or drug resistant seizures.—Adult-onset seizures due to neoplasm are often controlled initially with anticonvulsant drugs. If seizures recur after months or even years of adequate control, and no obvious cause is apparent (such as failure to take drugs or prolonged sleep deprivation), a tumor should be suspected. If anticonvulsant drugs are ineffective in controlling seizures and no obvious cause exists, more elaborate studies such as arteriography or pneumonencephalography may be indicated.

Appearance of new seizure type or change in pattern of seizures.—Seizures are typically stereotyped in their clinical presentation and usually remain so, with minor variations, for long periods. If the seizure pattern changes significantly or a new seizure type appears, a neoplasm may be present. We recently saw a 40-year-old man with a ten-year history of partially controlled psychomotor seizures characterized invariably by an aura of "burning rubber." When the aura changed to one of "rotten apricots," an arteriogram was performed and revealed a temporal lobe mass. An astrocytoma was found at operation.

Seizure patterns may change significantly when new anticonvulsants are added. Generalized tonic-clonic seizures may follow ethosuximide (Zarontin®) therapy in children with petit mal; psychomotor seizures may be altered by a variety of anticonvulsants and acetazolamide (Diamox®) has produced akinetic seizures in several of our patients with mixed seizure disorders.

Tumor should be suspected when seizures that previously occurred only at night begin appearing during the day, or when focal seizures begin incorporating more portions of the body with each attack.

Postictal (Todd's) paralysis may follow a focal or generalized seizure. It confirms the focal origin of the epileptic process and is useful historical information in patients with generalized seizures. If Todd's paralysis appears in an epileptic who has never previously experienced such postictal signs or if the postictal weakness or sensory disturbance becomes more extensive or long-lasting, an evaluation for tumor should be considered.

Electroencephalogram.—If focal slowing or other disturbances of background rhythms appear in an area previously containing only epileptiform activity or in a previously normal background, a progressive mass lesion may be present. One must be cautious not to attribute focal slowing to a tumor if the patient had a seizure just before the tracing. In such cases, an EEG should be obtained two to three weeks later; if slowing persists, further evaluation is warranted.

Anticonvulsant Drugs

Diphenylhydantoin

Diphenylhydantoin (Dilantin®, phenytoin, DPH) has become one of the most frequently used anticonvulsants since its introduction in 1938 by Merritt and Putnam.[54] It is effective in controlling generalized tonic-clonic (grand mal) seizures, focal cortical seizures and the variety of tonic seizures associated with the petit mal variant syndrome. It is less effective against psychomotor and photic-induced seizures and of little use in treating true petit mal or drug withdrawal seizures. The drug has no use in the prophylactic treatment of febrile seizures.[25]

The renewed interest in this drug can be attributed to two recent developments: (1) practical methods for determining the DPH concentration in biological fluids have allowed investigators to correlate seizure control and toxic symptoms with the amount of drug ingested and serum drug levels, and (2) the protean effects of DPH on many tissues outside the nervous system have become apparent over the last several years. DPH may have a toxic effect on connective tissue, bones, liver and the hematopoietic, cardiac, endocrine and lymphatic systems. This discussion will be limited to these two areas because of their practical clinical implications, and the reader is referred to other texts for details on the neurophysiological and neurochemical effects of this drug.[4,55,56]

The Relation of Serum DPH Levels to Seizure Control and Toxicity

Serum DPH *determination.*—Most laboratories now use either modifications of the original colorimetric method of Dill et al described in 1956[57] or modified gas chromatographic procedures. The accurate determination of DPH in human plasma, particularly in epileptic patients consuming many drugs, is difficult and the physician should scrutinize the results he obtains before relying on a single hospital or commercial laboratory. It has been our experience that a single blood specimen analyzed in several laboratories may yield widely divergent DPH levels. A clinical pharmacologist should be consulted if the serum levels correlate poorly with the clinical situation or unreliable values are obtained.

Absorption.—DPH is almost completely absorbed from the intestinal tract, bound to serum protein (90 percent) and metabolized by the liver predominantly to 5-phenyl-5' parahydroxyphenylhydantoin (HPPH), the latter appearing in the urine in amounts of about 65 percent of the daily DPH intake. As DPH is poorly water-soluble, little of the unmetabolized drug appears in the urine. The absorption of DPH following intramuscular injection was initially thought to be poor with unpredictable blood levels.[58] However, in a recent study, blood levels comparable to those following oral administration were found following intramuscular injection.[59] The drug half-life following oral administration is approximately 22 hours[60] and following intravenous injection, 10 to 15 hours.[61] [See addendum.]

After daily oral or parenteral administration, the drug level increases and finally stabilizes, remaining remarkably constant with a fixed daily intake. If the dose is increased, the serum concentration will increase and again stabilize at a higher level. The urinary output of HPPH remains nearly constant at 60 percent of the DPH intake regardless of the dose, evidence that the activity of the metabolic enzymes in the liver fluctuate according to the blood level. If this enzyme system is depressed, DPH will accumulate; if it is stimulated by other drugs (induction), the DPH level will decrease.

Therapeutic and toxic serum DPH *levels.*—The therapeutic blood level of DPH is usually stated as 10 to 20 μg per ml (1.0-2.0 mg per 100 ml). This level varies widely between patients; some will achieve control of seizures at values below 10 μg per ml whereas others require higher levels. The therapeutic range should be used as a rough guide for therapy; if seizures cease at levels less than 10 μg per ml, obviously no further drug increase is needed. Toxic symptoms usually appear at levels exceeding 30 μg per ml but individual sensitivities vary. In the original studies of DPH toxicity it was stated that a rough correlation existed between drug levels and toxic signs (lateral nystagmus occurring at serum levels of 20 to 30 μg per ml, gait ataxia at 30-40 μg per ml and lethargy or other disturbances of higher mental functioning at levels exceeding 40 μg per ml).[62,63] It should be emphasized, however, that the serum DPH concentration may reach toxic levels (>40 μg per ml) in some patients in the absence of signs of early toxicity (ataxia and nystagmus).[64]

The therapeutic blood level is usually achieved five to fifteen days following the beginning of therapy. If a further increase in dosage is made after a steady serum level is achieved, a second level will be reached in approximately the same time. The clinical response to DPH is therefore delayed and a waiting period of at least two weeks should follow each dosage increment. If the dosage is increased at shorter intervals, toxicity may ensue, as the drug accumulates.

If the physician wishes to obtain a therapeutic level more rapidly, he must give the patient a loading dose, the technique comparing with that of digitalization in congestive heart failure. The loading dose should consist of 1,000 mg of DPH given orally in a single dose or divided doses a few hours apart or by slow intravenous infusion (not to exceed 50 mg of DPH per minute).[63] This loading dose is followed by 500 mg in the second 24 hours and then regular maintenance doses of 300 to 400 mg per day. Daily serum dilantin levels may be used to monitor the adequacy of these doses. Higher blood levels may be needed at the beginning of therapy than will be required chronically; serum levels greater than 30 μg per ml are often needed to acutely control status epilepticus.

"Dilantinization" is necessary if DPH is to be effective in the treatment of status epilepticus or as a prophylactic drug in neurosurgery.

The maintenance dose of DPH in adults is usually 4 to 8 mg per kg of body weight daily.[65] It is not commonly known, however, that higher daily doses are required in children because they metabolize the drug at a more rapid rate. Children weighing 20 kg or less may require daily doses of 10 to 12 mg per kg.[66] The physician should warn the parents of epileptic children receiving DPH suspension that the bottle should be well shaken before each administration. DPH may be highly concentrated in the bottom of the unshaken bottle and toxicity develop as the last portions are administered. As soon as the children can swallow tablets, the suspension should be discontinued to prevent inadvertent toxicity.

Stable blood levels are obtained in most adults following once-daily administration.[67] Children under 12 usually require twice-daily dosage. The blood level in adults should be measured after several weeks of therapy and just before the daily dose (when levels should be at their lowest). Buchanan et al[67] found that the mean difference between peak and minimum DPH plasma levels in patients receiving once-daily doses was 2.4 μg per ml, a difference of little clinical significance. Once-daily administration is gratefully accepted by most patients, particularly those accustomed to carrying pills to work or school (similar dosage schedules may be applied to phenobarbital and perhaps other anticonvulsants, *vide infra*). A patient who inadvertently misses a daily dose should be instructed to double the dose the following day. With stable serum DPH levels obtained by once-daily administration the use of sustained release preparations appears unwarranted. Many physicians continue to advise the administration of sustained release capsules at bedtime. There is no pharmacological justification for the use of such preparations, which are usually more expensive than regular diphenylhydantoin capsules.[68]

Low DPH serum levels may be seen in many patients who claim that they are faithfully taking their daily medication. In the majority of patients, however, close questioning reveals that drug ingestion is sporadic and often the cause of poor seizure control. Many patients will manifest stable therapeutic levels with a change to once-daily administration and they can be instructed to have random samplings of levels at office or clinic visits to monitor their drug ingestion.

TABLE 2.—*Drugs That May Cause Elevation of Serum DPH Levels*

Name	*Reference*
isoniazid	Kutt et al[74] Brennan et al[75]
disulfiram (Antabuse®)	Olesen[76]
methylphenidate (Ritalin®)	Garretson et al[77]
chloramphenicol (Chlormycetin®)	Christensen and Skovsted[78]
chlorpromazine (Thorazine®)	Kutt and McDowell[63]
prochlorperazine (Compazine®)	Kutt and McDowell[63]
chlordiazepoxide (Librium®)	Kutt and McDowell[63]
diazepam (Valium®)	Vajda et al[79]
ethosuximide (Zarontin®)	Frantzen et al[80]

There are occasional patients whose blood levels are maintained below the therapeutic range on the usual maintenance dose. It has been reported that phenobarbital may induce liver enzyme systems, increase the rate of metabolism of DPH and shorten its half-life much as it does with sodium warfarin.[69] Kutt,[70] however, in reviewing the literature and his own experience, concluded that "the net effect of phenobarbital on the plasma level of DPH in the majority of patients is of small clinical consequence." Carbamazepine (Tegretol®) and ethanol have also been responsible for lowering the DPH serum level in a few patients.[71] DPH has also been reported to lower the serum levels of digitoxin and bishydroxycoumarin.[72,73]

Some patients are unable to tolerate the usual maintenance dose of DPH and toxic signs develop on doses of 200 to 300 mg daily. Three causes for low DPH tolerance have been reported: (1) congenital enzymatic deficiency—a rare familial deficiency of liver parahydroxylation enzymes which results in high DPH levels on DPH doses of 300 mg per day, (2) acquired liver disease such as severe cirrhosis or acute hepatitis, and (3) interference with DPH metabolism by other drugs.[63]

The daily dose of DPH should be reduced in patients with acquired or genetic defects of liver metabolism. We have recently seen a patient with psychomotor seizures in whom DPH toxicity developed six weeks following a temporal lobectomy while taking 300 mg of DPH daily, a dose well tolerated preoperatively. She was found to have hepatitis, probably secondary to the blood transfusions received at operation. Since recovery from the hepatitis, she has required only 150 mg of DPH daily to maintain her serum DPH level at 15 μg per ml.

Several drugs have been reported to increase serum DPH levels probably by inhibiting the metabolism of DPH in the liver. In some reports, this interaction was noted in a single patient and the frequency of occurrence in a large clinical population is largely unknown (see Table 2). The most extensively studied interaction is that between antituberculosis drugs, particularly isoniazid, and DPH. Brennan et al found that DPH metabolism was depressed in virtually all patients who could be classified as slow inactivators of INH (a genetically determined trait).[75] The degree of inhibition of DPH metabolism was proportional to the plasma INH concentration. The physician, therefore, should be aware of the drugs which interact with DPH and question all patients with unexpectedly high serum DPH levels about concomitant drug ingestion.

Toxicity of DPH

Toxic effects on the nervous system.—The syndrome of acute toxicity is well known (nystagmus, ataxia and an organic mental syndrome) and is dose related (*vide supra*). It is less well known that DPH toxicity may be manifested by an increase in seizure frequency and EEG deterioration,[81] focal neurological signs including hemiparesis, choreoathetosis,[82] elevated spinal fluid protein[83] and peripheral neuropathy.[84] Serum dilantin levels should be obtained from all epileptic patients with progressive neurological syndromes before more hazardous diagnostic tests are performed. The serum DPH level is usually more than 30 μg per ml in patients with these "pseudodegenerative syndromes." Regression of symptoms will occur after discontinuance of DPH.

Cerebellar ataxia is a common complication of DPH toxicity and usually resolves when the serum DPH level is reduced. Permanent cerebellar syndromes have been reported following DPH intoxication.[85] Animal studies have revealed degeneration of Purkinje cells and membrane proliferation with formation of bizarre bodies resembling those seen in the lipidoses after chronic DPH toxicity.[86] The Purkinje cell changes appear to be species specific, as no histological changes were produced by Dam[87,88] in experiments with pigs and monkeys. Dam also counted the number of Purkinje cells in the cerebellum of 32 patients with idiopathic grand mal epilepsy.[89] The loss of Purkinje cells was attributed to the severity and frequency of seizures rather than to the dose of DPH, suggesting that anoxia and perhaps other metabolic changes associated with severe seizures were responsible for the cerebellar disease.

The effects of DPH *on the secretion and metabolism of hormones.*—DPH administration may decrease the half-life of cortisol by stimulating hepatic metabolism and shift the metabolic pathway to 6 B-hydroxycortisol from the usual one of 17 hydroxy- and 17-ketosteroids, resulting in a decrease in the urinary excretion of the latter compounds.[90] It also increases the hepatic metabolism of dexamethasone (Metyrapone®) and shortens its half-life, thus reducing its suppression of adrenal cortical steroid production.[91]

Coma, secondary to hyperglycemia, has been attributed to DPH intoxication.[92] Recent metabolic studies have revealed that DPH may diminish the insulin response to glucose stimulation in man, probably through a direct effect of DPH on pancreatic release of insulin.[93] DPH should be used with caution in patients receiving diabetogenic agents or who have a risk factor for diabetes.

DPH *and calcium metabolism.*—DPH has significant and perhaps clinically important effects on calcium metabolism. Recent reports from England have described an increased incidence of hypocalcemia, elevated serum alkaline phosphate and, rarely, osteomalacia and rickets in epileptics treated with a variety of anticonvulsants, particularly phenobarbital and DPH.[94,95] The patients responded to vitamin D supplementation. Hahn et al[96] demonstrated significantly decreased serum 25-hydroxycalciferol in 33 percent of epileptic patients treated with combined DPH and phenobarbital. Their studies suggested that DPH accelerates the hepatic metabolism of vitamin D to inactive polar metabolites rather than the biologically active 25-hydroxycalciferol (similar to the effect of DPH on cortisol metabolism). They suggested that epileptic patients consuming anticonvulsant drugs should receive vitamin D supplementation. It is now our practice to measure serum alkaline phosphatase and calcium in all epileptic children; if serum calcium is diminished, vitamin D supplementation is recommended.

Effect of DPH *on thyroid function studies.*—Low serum PBI levels are frequently present in epileptic patients. This often leads to the diagnosis of hypothyroidism and the addition of thyroid extract to the chronic drug regimen. DPH is bound to albumin and alpha globulin, the same proteins which bind thyroxine and triiodothyroxine.[97] DPH will displace these thyroid hormones and lower the serum PBI or tetraiodothyronine (T4). If thyroid studies are performed in the DPH-treated epileptic, the physician should rely on those not associated with the protein bound hormone. The majority of epileptic patients referred to our clinic with the diagnosis of hypothyroidism are in fact euthyroid, DPH-depressed PBI levels having led to the erroneous diagnosis.

Effects of DPH *on hematopoisis.*—DPH may have adverse effects on the hematopoietic system.[98,99] It is not within the scope of this review to discuss these in detail, but certain aspects of the effects of DPH on folic acid metabolism deserve comment. Macrocytosis and, rarely, megaloblastic anemia have been associated with anticonvulsant drugs, particularly DPH and phenobarbital. Serum, red blood cell and cerebrospinal fluid folate are lower in drug-treated epileptic patients. It has been suggested that DPH may interfere with folic acid absorption.[100] Some investigators have claimed that some of the symptoms of DPH toxicity, especially dementia and psychosis, may be due to folate deficiency and are reversed with folate therapy.[101] Controlled studies of folate therapy in epileptic patients have not confirmed the improvement in mental status.[102] It has recently been claimed that folate therapy will reduce the more common signs of DPH toxicity such as nystagmus, ataxia and confusion.[99] The changes in higher mental functioning in epileptic patients, both treated and untreated, are complex and many etiologic factors are present. Further studies will be needed to evaluate the contribution of folic acid deficiency to these symptoms.

DPH may produce a syndrome resembling infectious mononucleosis or lymphoma ("pseudolymphoma").[103] Pseudolymphoma may clinically resemble malignant lymphoma and occasionally histological differentiation is difficult. The benign syndrome consists of lymphadenopathy, a morbilliform rash, fever, joint pain, hepatosplenomegaly and eosinophilia. Symptoms regress after DPH therapy is discontinued. Recent studies, however, have suggested a relationship between DPH and malignant lymphoma. A retrospective study by Anthony[104] revealed that epileptic patients receiving DPH have a much higher chance of developing lymphoma than the average population. Hyman and Sommers[105] described six epileptic patients receiving anticonvulsants in whom Hodgkin's disease or lymphosarcoma developed. The significance of these reports must await further large population studies; the relationship between chronic DPH therapy and malignant disease of the lymphatic system is still unclear.

Effects of DPH *on connective tissue.*—DPH has significant effects on connective tissue metabolism including an increase in insoluble collagen, increase in the rate of keratinization and loss of triglyceride and neutral fats.[106] DPH will stimulate fibroblastic proliferation in tissue culture. It has been recently suggested that the coarse facies seen in some chronic epileptics may be due to the effect of anticonvulsants on connective tissue.[107] The same study confirmed previous reports of calvarial thickening in skull x-rays of epileptic patients and suggested that DPH's effect on bone and connective tissue may be a causative factor.[108] Gingival hyperplasia, a common DPH side-effect, may be related to the ability of this drug to increase fibroblast growth. The gingival effects, possibly caused by the high DPH concentration in saliva, can be minimized by good oral hygiene. No other therapeutic regimen has been effective in controlling these gingival changes. If it becomes excessive, DPH may be replaced by ethotoin (Peganone®) or mephenytoin (Mesantoin) which have less tendency to cause gingival changes.

Miscellaneous toxic effects.—DPH has infrequently been associated with dermatosis such as erythema multiforme,[109] exfoliative dermatitis[110] and Stevens-Johnson's syndrome.[111] Hepatitis[110,112] and system lupus erythematosus[111,113] have also been attributed to DPH.

Phenobarbital

Phenobarbital is the most commonly used anticonvulsant drug. It is particularly effective in generalizing major motor seizures, focal cortical seizures and tonic seizures. It is less effective in psychomotor seizures, photic-induced seizures, drug withdrawal seizures and petit mal. Many neurologists initiate antiepileptic therapy with phenobarbital regardless of seizure type. Patients with allergic sensitivity to barbiturates, some hyperactive children and patients with severe respiratory and hepatic disease should be excluded. It has recently been reported that chronic oral phenobarbital significantly lowers the incidence of recurrence of febrile seizures if the serum phenobarbital level is maintained above 1.5 mg per 100 ml.[26]

Absorption.—The drug is slowly but completely absorbed from the gastrointestinal tract. Complete absorption probably follows intramuscular administration but quantitative data are not available. The drug is metabolized by the same liver enzyme system responsible for the biotransformation of many other drugs including DPH. The phenobarbital half-life is variable, ranging from 53 to 140 hours.[114] The drug is distributed to all body tissues and crosses the placental barrier to reach significant levels in the fetal brain.[115] The serum concentration may be altered by changes in blood pH; for example, acidosis increases the amount of unionized drug, thereby increasing the amount of drug entering the brain. Alkalosis will increase the amount of ionized drug and has been a useful adjunct in the therapy of barbiturate overdose.

Interaction with other drugs.—Phenobarbital will interfere with the metabolism of many drugs, including DPH. Coumadin blood levels are decreased by phenobarbital and higher oral doses are needed to reach therapeutic levels. If the same dosages are continued after phenobarbital is withdrawn, toxic coumadin levels may be reached and bleeding occur.[116] There is also evidence suggesting that phenobarbital will increase the metabolism of digitoxin and griseofulvin.[117] The inductive properties of the drug have been used therapeutically to lower bilirubin levels in jaundiced infants.[118]

Serum levels and seizure control.—There is less correlation of serum level and seizure control with phenobarbital than is present with DPH. The therapeutic blood level is approximately 1.0 to 2.0 mg per 100 ml and toxic symptoms are usually not seen until the level exceeds 3.0 mg per 100 ml. Many epileptic patients require blood levels exceeding 3.0 mg per 100 ml before seizure control is achieved, and it is not unusual to obtain levels of 5 to 7 mg per 100 ml in epileptic patients receiving chronic phenobarbital without obvious signs of toxicity. The physician should be hesitant to incriminate phenobarbital in the grossly intoxicated epileptic patient consuming several drugs if phenobarbital blood levels are below 6.0 mg per 100 ml. We have seen blood levels exceeding 15.0 mg per 100 ml in epileptic children who are still easily arousable. (Such levels would be associated with a very high mortality in the acutely intoxicated patient.) A daily dose of 1 to 2 mg per kg of body weight will produce therapeutic blood levels (>1.0 mg per 100 ml) in the adult in two to three weeks.[119] Higher daily doses are required in children to produce similar levels. Status epilepticus in the adult necessitates higher initial doses to reach therapeutic serum levels (10 mg per kg for two days will produce therapeutic blood levels within 12 hours).[120] The individual variability is great, however, and the physician should rely on the patient's clinical response rather than the serum blood levels to determine optimal dosage.

There is little variation in the serum blood level following once-daily dosage in adults and twice-daily administration in children (below 30 kg).[66] In some children, however, drowsiness may develop on twice-daily administration. Buchthal and Lennox-Buchthal[120] recommend giving such children two-thirds of their daily dose at night, but increasing the amount so that maximum blood level approximates 2.5 mg per 100 ml. Therefore, even a 30 percent decrease in serum level before the next dose would not bring the level below the therapeutic range.

Toxicity.—Phenobarbital will produce many of the toxic symptoms previously described with DPH. These include megaloblastic anemia, hepatitis, dermatosis and signs of acute toxicity such as nystagmus and ataxia. Sedation may develop during the first week of phenobarbital therapy but usually disappears with continued administration. Many of the epileptic patients with osteomalacia described by Dent[94] were receiving both phenobarbital and DPH. Phenobarbital often causes a paradoxical response, both in children (particularly those with organic hyperkinesia) and in the elderly, that is characterized by excitement and occasionally acute brain syndromes. It may rarely produce a lupus erythematosus syndrome and many immunologists have been hesitant to administer it to patients with established lupus erythematosus.

Mephobarbital (Mebaral®)

This drug is poorly absorbed from the gastrointestinal tract and the usual clinical dose is approximately twice that of phenobarbital.[121] It is almost completely metabolized to phenobarbital, which is probably the active compound. It is often stated that mephobarbital will produce less hyperactivity in children and is associated with fewer side effects than phenobarbital. This is most likely due to the lower phenobarbital blood levels produced by mephobarbital given in equimolar doses. It is our feeling that this drug, which is more expensive than phenobarbital, has no place in the treatment of epilepsy.

Methabital (Gemonil®)

This commonly used barbiturate is almost completely metabolized to barbital by the liver.[121]

There is no evidence to suggest that it has advantages over phenobarbital and sedation appears to be more prominent.

Primidone (Mysoline®)

This drug is recommended for the treatment of psychomotor seizures and is effective also against major motor and myoclonic seizures, where it is usually combined with DPH.[122] The drug is metabolized to phenobarbital and phenylethylmalonamide (PEMA). The mean half-life for primidone is 6.5 hours ± 1.0 hour with a range of 3.3 to 12.5 hours.[123] After an initial dose of primidone, PEMA rapidly appears in the serum and has a half-life approximating six hours.[124] Phenobarbital can be detected after chronic administration, appearing about three to four days after the initiation of therapy.[125] The earlier studies of primidone suggested that its anticonvulsant properties were due solely to the phenobarbital produced by its metabolic transformation.[126] More recent studies in animal and man have conclusively shown that primidone has anticonvulsant properties beyond those attributed solely to phenobarbital.[125,127] Indeed, it now appears that PEMA has anticonvulsant properties independent of phenobarbital and that doses of PEMA at less than anticonvulsant levels will augment the anticonvulsant properties of phenobarbital.[124]

The major side effects of primidone are sedation, nausea and vomiting and personality changes. Sedation may appear within the first 12 to 24 hours after the acute administration of the drug, before significant PEMA and phenobarbital serum levels can be detected, suggesting that primidone itself is the responsible compound.[125] The drug may infrequently cause megaloblastic anemia, folic acid deficiency, vitamin K deficiency in the newborn,[128] various dermatoses and, rarely, lupus erythematosus.[129] We have seen a lupus-like syndrome develop in identical twin sisters receiving primidone for myoclonic seizures (unpublished observation). Nursing mothers treated with primidone may secrete significant quantities in their milk and produce sedation in their newborns.[130] It has also been suggested that pregnant women receive vitamin K supplements to prevent hemorrhagic syndromes in the newborn, though the incidence of this toxic effect in children is unknown.[128]

The milder side effects can often be averted by low initial doses (often 50 mg per day) and gradual incremental doses to therapeutic levels (750 to 1,000 mg per day). The therapeutic dose for children is approximately one-half the adult dose (250 mg) but we have seen many children over the age of six tolerate full adult doses. The drug is usually given two or three times a day. Most laboratories do not have the facilities to measure serum primidone levels. However, the physician may measure serum phenobarbital to determine if the patient is actually taking primidone.

Ethosuximide

Ethosuximide (Zarontin®) is the drug of choice for petit mal seizures and may also be effective in the treatment of minor absences associated with atypical petit mal, myoclonic seizures and occasionally photic-induced seizures.[131] It is rapidly absorbed from the gastrointestinal tract and has a half-life of approximately 60 hours in adults and 30 hours in children.[132] The long half-life has suggested that once-daily dosage may be feasible. A recent study by Buchanan and Smith[133] revealed that relatively stable blood levels were obtained in adults receiving once-daily ethosuximide. Clinical studies of the effect of once-daily administration on seizure control have not been performed.

Serum ethosuximide levels can be obtained in some laboratories. There is a correlation between plasma level and dose but large variations occur between patients on the same dose. The therapeutic serum level appears to vary widely between patients. Sherwin and Robb[134] reported that blood levels above 40 μg per ml were needed to achieve complete seizure control in approximately 93 percent of their patients with petit mal.

Treatment is initiated with one capsule (250 mg) a day and increased by one capsule a day every eight to ten days, until seizures are controlled or toxicity develops. The slow rise in the plasma level after once-daily or twice-daily dosage indicates that increments in dose should be made slowly.[132]

Ethosuximide is a relatively non-toxic drug, though some patients will complain of sedation, nausea and vomiting and occasionally hiccoughs. Blood dyscrasias, dermatoses and, rarely, cases of lupus crythematosis have been reported.[135] Weinstein and Allen reported a 7 percent incidence of leukopenia in their series of 87 patients but medication was continued in all but one child; the leukocyte count returns to normal in those who continue to take the drug.[136]

Trimethadione (Tridione®)

Trimethadione is effective against petit mal seizures and occasionally against other minor seizures including myoclonus and photic-induced. It is almost completely metabolized to dimethadione, which may be the major therapeutic compound.[137] The therapeutic blood level has not been established. Clinical control appears to be better correlated with dimethadione serum levels, which cannot be measured in most clinical laboratories at present.

Trimethadione should only be used in the treatment of petit mal epilepsy when less toxic drugs are ineffective (ethosuximide or clonazepam). The most frequent toxic signs are sedation, dizziness and hemeralopia. The latter is due to the direct effect of trimethadione on the retina, causing visual impairment in high illumination.[138] It disappears slowly after discontinuance of the drug. Paramethadione (Paradione®), which has less retinal toxicity, may be used to replace trimethadione in these children. Of more importance, trimethadione may cause blood dyscrasias including isolated thrombocytopenia. Frequent blood cell counts including platelet counts should be obtained periodically in children receiving this drug.[139] The drug has also caused the nephrotic syndrome,[140] myasthenia gravis with a lupus erythematosus syndrome[141] and alopecia.[142]

The daily dose of trimethadione is approximately 30 mg per kg of body weight. Children will usually tolerate 300 to 1,500 mg given in divided doses.

Diazepam

Diazepam (Valium®) is an effective drug in the treatment of status epilepticus.[143] It is less known that the drug is also effective orally in the long-term treatment of epilepsy. It is well absorbed from the gastrointestinal tract but must be given three times a day due to its rapid metabolism. The drug is effective against various types of seizures including petit mal and psychomotor epilepsy, but must usually be given in combination with another drug such as DPH.[144] We have controlled epilepsia partialis continua in two children with a combination of carbamazepine (Tegretol®) and diazepam.

The drug is relatively non-toxic and has been the drug of choice in our clinic if seizures are not controlled with the standard first order of drugs—that is, DPH, phenobarbital, primidone and ethosuximide. Many patients will complain of dizziness and sedation if they are acutely started on full therapeutic doses (5 to 20 mg per day, depending on age). In these cases, diazepam is started at low doses (2 mg per day) and gradually increased over a period of several weeks. We are now treating several patients with doses exceeding 40 mg per day without obvious toxicity.

The drug has few serious toxic effects, though commonly causing dizziness, ataxia and sedation. Its use and toxicity in the acute treatment of seizures will be discussed in the section on status epilepticus.

Carbamazepine (Tegretol®)

Carbamazepine is an effective drug in the treatment of trigeminal and glossopharyngeal neuralgia, the crisis of tabes dorsalis, the painful paresthesias of certain myelopathies and occasionally post-herpetic neuralgia. It is also an effective anticonvulsant, used extensively in Europe, but has not yet been officially recommended in this country for use in the treatment of epilepsy. It is effective against many seizure types, particularly psychomotor and generalized tonic-clonic seizures.[145,146] It also has psychotropic effects, particularly in patients with phasic mental states.[145] Many side effects have been reported with this drug, and the physician should be familiar with these before using it. He should also be familiar with the Food and Drug Administration's regulations concerning the use of drugs for unapproved indications.[147]

RO5-4023 (Hoffman-LaRoche) (Clonazepam)

This new benzodiazepine derivative is under investigation in this country for the treatment of various seizure types. Preliminary reports suggest that the drug is effective against petit mal, myoclonic seizures including photic-induced, partial seizures of cortical origin and intravenously against status epilepticus.[148-150] We have found the drug to be effective against petit mal, myoclonic and other partial seizures in a small series of children who have been refractory to all other anticonvulsants (unpublished observations). The drug is effective in very low dosages (3 to 6 mg per day) and has no serious toxicity. Sedation, dizziness and ataxia are commonly seen at higher doses and personality changes and psychotic behavior have occurred in a few children. The drug appears to be a useful addition to the anticonvulsant armamentarium but is not yet available commercially.

General Principles of Chronic Drug Therapy in Epilepsy

After the physician has established that the patient has a seizure disorder that is probably not treatable by other means, he should initiate therapy with the appropriate anticonvulsant drug. He should be familiar with the drug's pertinent clinical pharmacologic properties, and particularly the common side effects and toxicity. The following general principles of therapy have been helpful to us in the management of epileptic patients:

1. Therapy should be initiated with a single drug. It has been our practice to begin treatment (regardless of the seizure type) with phenobarbital, an inexpensive and relatively non-toxic drug. Even petit mal seizures occasionally respond to this drug. It has been suggested that patients treated with phenobarbital and ethosuximide are less likely to develop generalized tonic-clonic seizures in adolescence than are children treated only with ethosuximide.[151,152] If phenobarbital proves ineffective or the seizures are not completely controlled, a second drug, appropriate to the seizure type under treatment, is added. If the seizures cease after the addition of the second drug, phenobarbital may be gradually decreased and discontinued if seizures fail to recur. If the seizures had been partially controlled with phenobarbital, both drugs should be continued.

2. The dose of each drug should be increased slowly according to its known half-life until seizures are controlled or toxicity appears. Serum levels of each drug should be determined but they should serve only as rough guides to dosage and the adequacy of patient consumption, and also to uncover the rare case of faulty hepatic metabolism.

3. The daily drug regimen should be adjusted to the known pharmacological features of each drug—there is, for example, little pharmacological sense in advising a patient to take DPH or phenobarbital three or four times a day. Not often is there reason to give an epileptic patient both primidone and phenobarbital, for the latter is a metabolic product of primidone. However, we do have a few patients with severe seizure disorders who require both drugs because high phenobarbital levels cannot be reached with primidone alone due to its toxicity.

4. The physician should methodically try every known anticonvulsant in patients with refractory seizures. We have treated many patients successfully with mephenytoin (Mesantoin®) when DPH or ethotoin (Peganone®) has failed. Drugs that are not specifically recommended for a certain seizure type are occasionally effective—ethosuximide for psychomotor seizures, for example. New drugs should be added in the order of their toxicity, reserving the most toxic drugs for patients with otherwise refractory or incapacitating seizures. A patient with a few minor seizures a day while taking ethosuximide should probably not be given carbamazepine or even trimethadione unless the risk of toxicity appears warranted. The seizures should not be controlled at the expense of chronic toxicity (see section on psychiatric aspects of therapy).

5. Periodic physical examinations, in conjunction with hematological studies, should be performed on all patients receiving chronic anticonvulsant drugs. The physical examination should include not only a search for signs of toxicity but a detailed neurological examination. Most patients with adult onset seizures, particularly those with focal seizures or focal EEG abnormalities, should be considered "tumor suspects." A long history of seizures should not lull the physician into a state of complacency. We have seen several patients in whom neoplasms were not found until after more than ten years of seizures.

The laboratory studies should be performed frequently at the beginning of therapy with a new drug. Carbamazepine, for example, may cause leukopenia within the first week of therapy. This usually resolves within several weeks but may progress to levels necessitating discontinuance of the drug. The laboratory examination should be designed to include any unique toxicity of the drug in question. Urinalyses are mandatory in all patients taking trimethadione; liver function studies should be obtained in patients receiving carbamazepine, the hydantoins, or the like. A platelet count should be included with the complete blood cell count, as thrombocytopenia may be the initial manifestation of the hematopoietic toxicity of drugs such as trimethadione. Laboratory studies should be obtained periodically in all patients regardless of the duration of therapy. Mephenytoin (Mesantoin®) toxicity, for example, may not appear until one to two years after the initiation of therapy.

Patients should be instructed to report immediately any change in their health such as the appearance of purpura, easy bruising, bleeding gums, jaundice, fever, recurrent infections, or dermatosis.

6. Periodic electroencephalograms should be

obtained, particularly in patients with adult-onset seizures. The appearance of focal slow activity, despite continued seizure control, should alert the physician to the possibility of an expanding lesion and prompt further studies such as a brain scan or skull x-ray study.

7. When seizure control is maintained for two years, the physician should consider discontinuing medications after weighing the various factors involved.

8. The physician should acquaint himself with the motor vehicle operation laws as they concern epileptics. In California it is the duty of the physician to report all epileptic patients to the Motor Vehicles Department and to supply periodic reports on the patient's condition. There is implication that the physician who fails to do so may be liable for his patient's actions on the highway.

Surgical Therapy

A small proportion of patients with intractable epilepsy can be dramatically helped by surgical operation. Seizures arising from epileptogenic tissue in the temporal, frontal and occasionally parietal lobes are most amenable to surgical resection. Children with infantile hemiplegia and body hemiatrophy often have refractory seizures and severe behavior disorders. The removal of the involved hemisphere (hemispherectomy) is usually followed by dramtic improvement in behavior and reduction in seizure frequency.[153] A recent report on the long-term follow-up of patients who had undergone hemispherectomy revealed that complications attributable to the operation developed in about one-fourth of them, frequently many years afterward.[154] Despite this relatively high complication rate, this procedure is still indicated in children with refractory seizures due to the cerebral hemiatrophy syndrome.

Temporal lobectomy is the single most common type of operation done for relief of seizures. The anterior portion of the temporal lobe is surgically accessible and can be removed with minimal morbidity or significant long-term sequelae.[155] Temporal lobectomy should be reserved for patients with medically refractory psychomotor seizures that are socially and economically disabling. The criteria used at Stanford for selection of candidates for temporal lobe operation are: (1) continuing disability from severe seizures despite adequate medical therapy; (2) consistent localization of interictal epileptiform discharges to one temporal lobe; (3) electroencephalographic demonstration that ictal activity associated with the patient's typical clinical seizure arises from the same region; (4) absence of significant psychiatric disease, particularly psychosis; and (5) absence of generalized epileptiform activity on serial EEGs unless preceded by focal seizure discharge in the temporal lobe.

Complete delineation of the electroencephalographic characteristics of the seizure may require epidural or depth electrode recordings, prolonged recording sessions and, in some patients, chemical activation with intravenous pentamethylenetetrazol (Metrazol) or tripelennamine (Pyribenzamine®).[156] The fifth criterion represents a complex problem in EEG interpretation that will not be discussed in detail here; the reader is referred to a recent article specifically directed to the significance of co-existing focal and diffuse paroxysmal discharges in the EEG of epileptics.[157]

The results of surgical treatment of patients with unilateral temporal lobe foci have been gratifying. Approximately 75 percent have complete alleviation or significant reduction of seizures, and partial improvement is obtained in the majority of the remaining patients. Surgical results are less impressive in patients whose preoperative EEGs reveal bilateral, independent temporal lobe foci, indicative of separate lesions. Stereotactic implantation of depth electrodes is needed to evaluate these patients before it can be concluded that the clinically significant focus is confined to one temporal lobe.[158] The postoperative management of patients, even if seizures are no longer present, is frequently complicated by significant psychological problems which will be discussed in a later section.

Temporal lobectomy is usually performed on adults or occasionally patients in their late teens. Falconer, however, in his series of 100 consecutive patients, operated on nine children under the age of 15 with excellent relief of seizures and less striking improvement in behavior and social adaptation.[159] Temporal foci in younger children may represent the electroencephalographic manifestation of a diffuse, hereditary seizure disorder[33] and surgical intervention is contraindicated. There are EEG and clinical criteria for distinguishing the hereditary temporal foci from those that arise from focal temporal lobe diseases and perhaps operation should be considered at an earlier age in more children with refractory psychomotor seizures before severe behavioral or intellectual deterioration occurs.

There is no doubt that surgical therapy for intractable temporal lobe seizures, and other types of focal epilepsy, has been successful in alleviating seizures or significantly reducing their frequency.[17,159-162] However, one would anticipate that this kind of therapy, with its obvious risks and possible long-term sequelae, will gradually disappear from the therapeutic armamentarium of epilepsy as more effective drugs are developed. For the present, however, every patient with seizures refractory to drugs should be evaluated for surgical treatment. The majority, of course, will be denied operation because they have generalized seizures or focal epilepsy located in areas inaccessible to the surgeon or because of the other reasons previously discussed. The dramatic effects of operation in previously incapacitated epileptic patients is evidence that this mode of therapy still plays an important role in our efforts to control epilepsy. It is obvious that operations of this type should be performed only in centers with wide experience in this form of therapy.

Status Epilepticus

The term *status epilepticus* is defined according to the system proposed by the International League Against Epilepsy and ". . . is used whenever a seizure persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring epileptic condition. . . "[15] This classification divides status epilepticus into (1) generalized status epilepticus (generalized convulsive states—grand mal, tonic, clonic and myoclonic, and nonconvulsive generalized status —petit mal status), (2) unilateral status epilepticus—usually seen in children as hemiclonic attacks and often followed by transient or permanent hemiplegia,[163] (3) partial status epilepticus—often seen in adults and consisting of focal motor or less frequently, focal sensory status. Epilepsia partialis continua is best included under this heading and consists of constant focal motor seizures lasting for hours, days or even weeks, often localized to unilateral muscle groups, including a single extremity or even one digit, and tending not to spread. Some patients may be comatose but others are conscious and ambulatory.[164,165]

Status epilepticus in an adult has a significantly different connotation from that occurring in a child. If patients with acute head injury are excluded, a definite cerebral cause for the seizures can be determined in approximately 60 percent of adults[166] and 53 percent of children.[167] Over one-half of the children in whom status epilepticus occurs without obvious central nervous system disease are febrile. Rose and Lombroso[168] were unable to determine a cause in 28 percent of newborns with seizures. In children, status epilepticus may frequently be the initial manifestation of chronic idiopathic epilepsy (36 percent),[167] whereas in adults this is rarely the case. In neonates and children, the causes are numerous[167,168] and will not be discussed in detail here, except to emphasize that tumors are rarely present (no tumors were found in Aicardi and Chevrie's series of 239 cases of status epilepticus in children[167]). In adults, however, the most common etiologic factors in the symptomatic cases are cerebrovascular disease, neoplasms, trauma and central nervous system infections. In some medical centers, post-anoxic encephalopathy, which may complicate cardiopulmonary bypass procedures, and metabolic encephalopathy are frequent causes of status epilepticus. Approximately 10 percent of patients with status will die during the acute phase of the illness, usually from the underlying central nervous system or systemic disease rather than the seizures *per se*. Approximately one-third of children with status epilepticus will be left with permanent neurological signs and in about 50 percent of these no cause other than the status can explain the neurological deficits.[167]

The electroencephalogram may be useful in the initial evaluation and management of a patient with status epilepticus. In neonates, seizures are often "fragmentary,"[168] consisting of movements of single limbs, migrating clonic activity which may resemble the tremulousness of normal infants, brief tonic episodes and, occasionally, apnea. The EEG may be helpful in confirming the epileptic basis for a child's intermittent movements or disturbed behavior. In some patients, such as those with tonic status epilepticus, the clinical seizures may gradually disappear but electrographic status persists. Autonomic disturbances, such as instability of the blood pressure and temperature regulation, may increase and death occur from circulatory collapse. Occasionally epileptic patients, usually children, will have deterioration of mental function or stupor or so-called "pseudo-dementia" or "pseudo-ataxia." Drug intoxication is often suspected but the EEG will reveal the characteristic patterns of status epilepticus.[169] Frequently the EEG will reveal focal abnormalities that were not suspected clinically and provoke further diagnostic procedures such as cerebral arteriography. In adults with status epilepticus due to focal cerebral disease there is a striking frequency of localization in the frontal lobe.[170,171] This area may be relatively "silent" clinically and the EEG then may be the first indication of localized disease in this area. Periodic lateralized epileptiform discharges (PLEDS) are a relatively stereotyped EEG pattern not uncommonly seen in patients with status epilepticus.[172] They are most commonly associated with cerebral infarction, either thrombotic or embolic, central nervous system infection, usually herpes simplex encephalitis and, less frequently, neoplasms, trauma and subdural hematomas. (Readers interested should refer to the bibliography for further details of the electroencephalographic patterns of status epilepticus.[163,165,168-174])

The physician should approach the patient with status epilepticus in the same manner as he would any patient with acute onset of a central nervous system lesion. In the adult patient the initial evaluation should include diagnostic studies for infectious processes, such as lumbar puncture and viral serological tests, including heterophile agglutination for infectious mononucleosis; blood should be drawn immediately for determination of serum electrolytes, liver function tests, sugar and serum phenobarbital and DPH (if the patient is an epileptic who is presumably taking these drugs). If the DPH and phenobarbital serum levels are low, it must be assumed that the patient has not taken his drugs faithfully or that another drug has increased hepatic metabolism (see section on DPH and phenobarbital). If status epilepticus occurred despite therapeutic DPH or phenobarbital levels, the physician should consider replacing these drugs in the patient's chronic regimen after control of the status is achieved. As discussed previously, toxic DPH levels may also lead to an exacerbation of seizures in some patients.[81] In neonates, serum electrolytes including calcium and magnesium should be determined, a lumbar puncture performed and blood cultures obtained. Toxicological studies, in conjunction with a detailed history from friends or relatives of possible toxin ingestion, should be obtained. This is particularly important in children without a history of seizures and in adolescents and young adults who have access to illicit drugs. An electrocardiogram should be obtained on all adults, as a cerebrovascular accident and subsequent seizures may be secondary to hypotension or an embolism from an acute myocardial infarction. A complete medical history should be obtained and a general physical examination carried out because seizures may be the initial presenting symptom of many medical diseases.

Treatment of Status Epilepticus

The treatment of the patient in status epilepticus depends on the type and duration of seizures and the general condition of the patient. Minor status epilepticus such as petit mal, focal sensory or psychomotor status does not usually represent a medical emergency and can be treated more slowly, occasionally with oral medication. The patients do not experience the anoxia and autonomic disturbances common with generalized motor seizures and should not be overtreated with large intravenous doses of potentially toxic anticonvulsants. There is no evidence that frequent minor seizures will cause pathological changes in the brain. Focal motor status may occur, however, in some patients whose general medical condition is so poor that prompt cessation of the seizures is desirable—for example, patients in the immediate postoperative period, those with acute cerebrovascular accidents, and patients with multiple injuries following trauma.

Generalized convulsive status, particularly tonic-clonic, tonic and frequently clonic seizures, should be approached as a medical emergency. The usual therapeutic measures employed in any comatose patient should be instituted—insertion of an oral airway and occasionally endotrachial intubation, frequent pharyngeal and tracheal suctioning, proper positioning to prevent aspiration, padding of the bed to prevent injury, and insertion of a padded tongue-blade to prevent injury to tongue and teeth. The padded tongue-blade, commonly seen in most hospitals attached to the patient's bed, should not be inserted into the patient's mouth during a seizure, for the maneuver is technically difficult and can cause unnecessary trauma. It should be inserted between seizures and so placed that it will not interfere with air exchange or suctioning.

Newborn.—Frequent seizures in neonates are usually caused by anoxia, trauma, infection, congenital central nervous system anomalies and metabolic encephalopathy.[168] The most common metabolic causes are hypocalcemia (particularly in premature infants), hypoglycemia, and very infrequently hypomagnesemia (occasionally without concomitant hypocalcemia) and pyridoxine deficiency or dependency. It has been our policy to initially treat all newborns with seizures with a sequence of intravenous electrolyte injections (after blood speciments have been drawn) and pyridoxine. Most infants will respond dramatically if an electrolyte deficiency exists. The pyridoxine deficient or dependent child may respond as rapidly, but some will require continuous pyridoxine infusion before seizures cease completely.[175] This rare syndrome and some of the aminoacidurias associated with seizures in the newborn period may be suspected or even anticipated if there is history of a similar neurological syndrome in a sibling or other relative. Further metabolic studies, including a 24-hour urine collection for a quantitative aminoacid determination, may be needed in evaluating these children.

The recommended therapy for neonatal seizures is a series of intravenous infusion, one given every 5 to 10 minutes with EEG monitoring. (The EEG is not required but is often helpful because electrographic status may persist despite the cessation of clinical seizures.)

1. Pyridoxine: 20 to 50 mg intravenously.
2. Magnesium sulfate, 1 percent: 10 ml per kg of body weight, injected slowly with EKG monitoring.
3. Calcium gluconate, 10 percent: 1 to 2 mg per kg of body weight injected slowly with EKG monitoring.
4. 50 percent glucose solution: 0.5 to 1 ml per kg of body weight.

If these infusions are ineffective, anticonvulsant drugs should be given immediately. Tracheal intubation should be performed before anticonvulsant therapy because the risk of apnea is high.

1. diazepam (Valium®): 0.1 mg per kg of body weight.
2. phenobarbital: 5 mg per kg of body weight acutely, total dose 12 mg per kg per 24 hours.
3. diphenylhydantoin: 10 mg per kg of body weight, orally or intravenously. This drug is rarely necessary in the treatment of neonatal status epilepticus and there is little information about its use in newborn infants.

If the seizures are not due to electrolyte imbalance, the child should be maintained on anticonvulsants for at least 12 to 18 months, depending on the cause of the status and subsequent neurological and electroencephalographic evaluations. The majority of infants will be controlled relatively easily in the acute period; those who die usually succumb to massive cerebral trauma or anoxia, severe infections or gross congenital anomolies.

The physician should be cautious in discussing the child's prognosis with the parents during the first six to twelve months of life, particularly in infants with intracranial birth injury, anoxia or infection. The EEG at the time of status epilepticus may be useful in predicting the child's future neurological condition. However, these records are difficult to interpret and should be read by an electroencephalographer with experience in pediatric EEGS.[168] Many infants after recovering from status epilepticus will appear neurologically normal, even to the pediatric neurologist, and have normal EEGS during the first few months of life, only to have a return of seizures later in the first year of life. The "normalization" of the EEG one to two weeks after successful treatment of status epilepticus is very common and may be seen in children who will eventually deteriorate neurologically or fail to reach normal milestones at six to twelve months of age.

It is often difficult to determine how long to continue anticonvulsant therapy in children with neonatal status. Most neurologists will continue drugs until at least one to two years of age. We have occasionally discontinued drugs at an earlier age if the child is developing normally, the EEG is normal and the neurological examination is normal. We have been impressed that many children with status epilepticus secondary to subarachinoid hemorrhage (SAH) have a very benign course and anticonvulsants can be withdrawn at eight or ten months of age (we have not attempted to withdraw drugs at an earlier age). Rose and Lombroso[168] noted no abnormality at follow-up in eight of nine children with SAH and status epilepticus.

Older Children and Adults

Diazepam.—2.5 to 30 mg intravenously[143,176] (not to exceed 10 mg in a child). This drug should be injected slowly; apnea or hypotension may result from rapid injection. Bell[177] noted that this complication occurs most commonly in patients who have already received phenobarbital or paraldehyde. Sharer and Kutt[178] found that the propylene glycol solvent in parenteral preparations, as well as diazepam itself, produced hypotension and respiratory distress in cats. Diazepam may occasionally precipitate status epilepticus in children with the petit mal variant (Lennox-Gastaut) syndrome.[179]

Phenobarbital.—10 mg per kg of body weight by mouth or 300 to 600 mg intravenously. One of the common errors in the treatment of status epilepticus is to give insufficient intravenous doses of phenobarbital. We have given doses up to 1,000 mg, particularly in patients already receiving the drug (see section on phenobarbital), without respiratory depression. The drug should be repeated at two- to four-hour intervals if seizures recur. After the seizures are controlled, maintenance therapy should be instituted. More studies are needed to evaluate the correlation between dose and serum levels following intramuscular administration.

Diphenylhydantoin.—This drug is commonly used in the treatment of status epilepticus but most physicians use doses that will not produce therapeutic serum levels acutely. One gram should be given slowly intravenously or by the intramuscular or oral route. Six hundred milligrams should be given the next day, followed by maintenance doses thereafter (see section on DPH). We have been using this drug more frequently in patients whose general medical condition is poor and when the respiratory depression of phenobarbital is to be avoided. Patients in whom status epilepticus develops in the immediate postoperative period, particularly after thoracotomy, and those with severe respiratory disease, cerebral trauma or debilitating diseases may respond to DPH.

Paraldehyde.—5 to 15 ml rectally in adults; 0.3 mg per kg of body weight rectally in children; 3 to 5 ml in 100 ml of saline solution intravenously (a glass syringe should be used, as paraldehyde is incompatible with many of the plastics).

The physician should persist with high dose anticonvulsant therapy for at least 12 to 24 hours. All too often, status epilepticus is stopped with a single injection of diazepam or phenobarbital and the patient then is given low dose maintenance therapy only to have seizures recur several hours later.

Steroids, particularly dexamethasone, have been recommended for the treatment of the cerebral edema associated with prolonged status epilepticus. There are many other metabolic and physiological changes which occur during generalized seizures in addition to an increase in intracranial pressure,[180] and the effectiveness of antiedema agents in reducing morbidity or stopping the seizures has not been demonstrated. Dexamethasone may be used if signs of increased intracranial pressure occur or if a shift of midline structures is demonstrated, as is occasionally seen in the acute infantile hemiplegia syndrome,[163] cerebral vascular thrombosis, infections such as herpes simplex encephalitis or other space-occupying lesions.

It has recently been reported that hypothermia, extravascular total body cooling with extravascular cooling of brain, is an effective adjunct in the control of refractory seizures and affords long-lasting seizure control.[181] Despite the apparent success of this procedure in a small group of patients, further studies are needed before it can be considered a practical clinical method.

If generalized motor seizures persist despite adequate medical therapy, the physician should not hesitate to utilize general anesthesia with fluothane or ether. Newer anesthetic agents should be avoided, particularly those with the capacity of inducing epileptiform activity in normal patients, such as ketamine.[182] If the physician uses adequate parenteral anticonvulsant drugs, however, anesthesia will rarely be needed. Though we treat large numbers of patients with status epilepticus every year at Stanford, general anesthesia has been needed only twice in the last six years, and in both cases was unsuccessful.

Psychiatric Aspects of Epilepsy

Since the first description of epilepsy centuries ago, the psycho-social aspects of seizures have been of abiding interest. This review cannot cover the many facets of this complex topic, but we will be concerned with some of the practical problems confronting the physician in his daily care of the epileptic patient—problems that are expected and can often be anticipated in a large percentage of epileptics, particularly afflicted children and adolescents. The reader interested in obtaining more information about this important field of epilepsy should refer to the bibliography (see refs. 183 to 191).

Seizure disorders beginning in the first or second decade of life have a particular impact since they occur at a time when the child is developing his own sense of self and establishing the personal security and self-confidence needed for normal mental development. In the first decade, the child is learning to interact with his peers and begins the slow process of separation from strong parental influences. Once he reaches adolescence, he is confronted with strong peer pressures and the need for acceptance by his contemporaries and he must deal with the reality of facing the world on his own. The intrusion of an illness, particularly a chronic and socially disabling one, into this complex scheme of development can often have devastating effects on the youngster's development.

All too often, physicians are simply concerned with the seizure disorder and approach the problem as an exercise in clinical pharmacology: Find the right drug and give enough to suppress the seizures. The disabling effects of the drug are frequently neglected, or accepted as inevitable, in the ensuing attempt to obtain complete seizure control. While this is a laudable goal, the child attempting to cope with the ridicule of his peers, the anticipation of his next seizure with its threat of bodily injury, or, at best, a period of bizarre behavior for which he is amnestic, must now deal with the effects of the anticonvulsant which can range from drowsiness to significant alterations of personality, behavior and intellectual function and concentration.

On another level, the parents of epileptic children are frequently frightened by an illness that is associated with many superstitions. They may be ashamed or guilty and perhaps apprehensive about the child's future. Many become over-protective and place restrictions on the child's mobility. These unreasonable restrictions are usually unwittingly reinforced by the limitations placed upon the child's activity by the physician. Many children are told to refrain from bike-riding or roller-skating, or are withdrawn from physical education classes at school and, in adolescence, prevented from entering competitive athletics.

Sometimes parents may suspect that the child is willfully producing the seizures, particularly if they are associated with bizarre or antisocial behavior. This concern leads to doubt in the child's mind as to the exact nature of his seizures and many come to believe their parents' admonitions that the attacks "are brought on" for the purposes of manipulating the situation. We have had parents relate that their child's propensity for early morning seizures is a ruse to avoid having to attend school or that seizures are used to avoid unpleasant household duties. This often leads to bitter family conflicts and may alienate the child from his parents and siblings.

On the other extreme the parents may become over-protective and avoid assigning household chores to the epileptic child and, in addition, lower their demands for his equal participation in family life. Coupled with this is often an unrealistic lowering of expectations for the child's behavior, which unfortunately only serves to reinforce the child's feelings of inadequacy and further to reduce his already low self-esteem.

Teachers often have little knowledge of epilepsy and are unable to cope with the epileptic child's disruption of normal class routine. Rather than educating themselves and the other children in the class about the true nature of the youngster's seizures, teachers and administrators often find it easier, and therefore less stressful, to place the child in special classes. Some epileptic children of normal or above normal intelligence find themselves in classes for retarded children or are relegated to a few hours a day of home tutoring.

Youngsters with epilepsy respond to these pressures in a variety of ways. Some become completely withdrawn, sever all close friendships and passively accept the restrictions placed upon them. They lose their self-confidence and initiative, develop into recluses, and give up any hope for further achievement. Another response to the restrictions and family attitudes is by "acting out." They become argumentative, disrupt school and family stability, become aggressive toward their peers and ultimately create a vicious cycle whereby increasing parental reprimand and punishment provoke further outbursts from the child. In this instance, it is critically important for the physician to consider the possibility that this irritable and negative behavior might be related to a side effect of the anticonvulsant medication.

An occasional child reacts to these unusual stresses with hysterical behavior. We have seen several youngsters develop typical hysterical "seizures" which may be difficult to distinguish historically from true seizures. This often leads to a faulty estimate of the seizure frequency, and to increasing doses of anticonvulsant drugs. Our strong impression is that these hysterical episodes are the only means by which the child can subconsciously control the world around him to achieve a modicum of self-esteem or gain the parental attention he so desperately desires. In actuality, unfortunately, this frequently leads to increased parental alienation.

One of the most fascinating aspects of the recent advances in the control of epilepsy is that some patients develop hysterical seizures and other emotional problems *when complete seizure control is finally attained.* This particularly seems to be the case with some epileptics who were poorly controlled or untreated for many years and then are unable to cope with the sudden cessation of seizures. We have found that this is a most complex problem and affects the patients in many ways. For example, the family might assume that the patient is now "cured" and capable of handling his full load of responsibility, even though for many years he was shunned and not expected to participate fully in the functioning of the family. He is now clearly unable to abruptly change his pattern of life to meet the demands of being "normal." We have seen this behavior in patients after successful temporal lobectomy, particularly in those whose seizures began in childhood. Such patients have developed their personalities in a "setting of epilepsy" and have not experienced the normal developmental tasks of the adolescent period which are so important in developing a strong ego and self-identity. We recently performed temporal lobectomy on a young woman with long-standing refractory psychomotor seizures. The patient returned to our clinic a month later, now seizure-free but complaining of paralysis and anesthesia of her right arm. Neurological examination revealed this to be a hysterical dysfunction. Under gentle questioning, the patient described increasing anxiety from the demands being placed upon her by her family, previously accustomed to her disability but now expecting her to assume the care of her infant son and full household duties. It is imperative that all such patients and their families receive expert counseling and close follow-up to prevent the development of psychiatric disorders, such as hysteria or depression, following control of long-standing epilepsy with drugs or by surgical operation.

It is apparent from these brief comments that psychological disorders are frequent concomitants of epilepsy. The physician should be prepared to discuss all aspects of the disorder with the patient and his family, referring them, if necessary, to a local chapter of the state epilepsy society for further assistance.* He should encourage the school authorities to continue the child in a regular school program, particularly if the seizures are infrequent and the child is of normal intelligence. We have found that a personal conference with school personnel, educating them on seizure disorders and the first aid treatment of the youngster who is convulsing, leads to rapid reintegration of the child into the classroom.

We feel that most children with minor seizure disorders should be allowed to participate in physical education classes and competitive sports. Such children should be encouraged to lead normal active lives within the limits imposed by their particular type of seizure. Parents should expect the child to assume an active role in family activities and perform his share of household chores.

The epileptic patient should be referred to a psychiatrist if the psychological difficulties continue to interfere with school performance or lead to increasing family strife. If the patient is to learn how to live with epilepsy, he must be offered all the resources available to his physician. His emotional difficulties should not be accepted as an inevitable and untreatable part of his seizure disorder. Frequently, the so-called "epileptic personality" represents the reaction of the individual to this socially unacceptable and frightening disorder and is eminently responsive to psychiatric therapy.

One last point that should be emphasized is that physicians should not substitute drug intoxication for complete control of seizures, unless generalized motor seizures or severe limbic system seizures are present. The child's performance in school and at home may improve dramatically if the dose of anticonvulsant drugs is reduced, despite occasional minor seizures. We have also found that adolescents do much better when they are encouraged to manage their own medication and report their progress directly to the physician, rather than through their parents.

ADDENDUM

Two recent articles* have clearly demonstrated the low serum DPH levels obtained following intramuscular administration. This route of administration of DPH should be avoided or the dose increased with appropriate monitoring of serum DPH levels.

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Refer to: Antibiotic therapy in compromised hosts—Medical Staff Conference, University of California, San Francisco. Calif Med 119:49-59, July 1973

Medical Staff Conference

Antibiotic Therapy in Compromised Hosts

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, CA 94122.

DR. MORRELLI:* *This morning we have asked Dr. David Drutz, Chief of the Infectious Disease Service at San Francisco General Hospital, to discuss an important problem in clinical pharmacology: The selection of antibiotics for therapy in compromised hosts.*

DR. DRUTZ:† In discussing the rational approach to antimicrobial therapy in the immune-compromised host, I think that it is important to remind ourselves why these patients should be singled out as presenting a unique problem in infection management. What are the special considerations which make our therapeutic approach to them any different than to other patients with infection? Before discussing therapy, however, I want to make it clear that we are far from an ideal situation with regard to *diagnosing* opportunistic infections in immune-compromised hosts. We must still biopsy the lung to make the diagnosis of Pneumocystis carinii infection with any degree of assurance, and the patients in whom we perform this procedure are far from ideal surgical candidates.[1] We still do not know how to diagnose systemic candidiasis with precision; agglutinins and precipitins, mycelial phase fungi in the urine, positive blood cultures—these things often confuse more than help us.[2] We do not know how to make the diagnosis of necrotizing encephalitis due to toxoplasmosis without biopsy of the brain, and we often confuse this process clinically with progressive multifocal leukoencephalopathy—another opportunistic infection due to a virus or viruses.[3,4] Hence, if I had not been asked to speak specifically about treatment of infection in compromised hosts, I would spend the majority of my time discussing the difficult problem of diagnosis of opportunistic infection. However, we shall assume for the sake of today's presentation that the diagnosis has been made. We shall not be concerned with the question of prevention of infection in immuno-

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TABLE 1.—*Special Considerations Influencing Approach to Treatment of the Infected Compromised Host*

1. Propensity to multiple simultaneous infecting microorganisms.
2. Necessity for unusual combinations of antimicrobials.
3. Limitations on use of indicated antimicrobials.
4. Indication for unfamiliar antimicrobials.
5. Indication for unfamiliar routes of antimicrobial administration.
6. Necessity for specific microbicidal therapy.
7. Avoidance of gross alterations of host microbial flora.
8. Avoidance of aggravation of existing problems.

suppressed hosts, although this is of critical concern, especially in dealing with a patient who is receiving cytotoxic drugs and has less than 1,500 circulating granulocytes per cubic millimeter of blood.[5,6] Finally, we shall not deal with the difficult philosophic question of how to approach the infection-susceptible patient who requires restoration of immune competence in order to survive, but who will die of his underlying disease if his immune status is restored.

To return to the original question: What are the special considerations which make our therapeutic approach to the compromised host different from that in other patients with infection? These are listed in Table 1.

1. There is a propensity to multiple simultaneous infecting microorganisms. It is not at all uncommon, for example, to encounter cytomegalovirus infection together with pneumocystosis or toxoplasmosis. Sometimes the situation is carried to extremes. Consider, for example, the therapeutic complexities implicit in the management of a renal transplant recipient with staphylococcal sepsis and pneumonia, nocardiosis, and active pulmonary tuberculosis, all occurring simultaneously. We encountered such a patient recently.

2. The necessity for the use of unusual combinations of antimicrobials is a direct consequence of number one. We have had many occasions to employ pentamidine isethionate, amphotericin B and one or another standard antibiotic simultaneously. The effects of such polypharmacy on drug efficacy are virtually unknown.

3. There are often limitations on the use of indicated antimicrobials. A frequent dilemma which we face is the necessity for using amphotericin B, which is quite nephrotoxic, in the renal transplant recipient who already has tenuous renal function.

4. Unfamiliar antimicrobial agents may be indicated. Two of these are pentamidine isethionate and 5-fluorocytosine, which we shall discuss today.

5. Antimicrobial agents must sometimes be given in unfamiliar ways. Typical examples are pentamidine and gentamicin which must be given intravenously to the severely thrombocytopenic patient who cannot tolerate intramuscular injections.

6. The necessity for specific microbicidal therapy applies to the practice of infectious diseases in general, but is critical in the immune-suppressed patient if therapy is to be successful. In these patients, remember, we usually cannot rely on cellular defense mechanisms to clear up residual foci of infection.

7. Avoidance of gross alterations of host microbial flora is critical if superinfection is to be avoided. This can be accomplished by avoiding excessive antimicrobial dosages and unduly prolonged duration of therapy. Further, we routinely employ oral nystatin in antibiotic-treated patients who develop thrush in an attempt to lower titers of fungi in the gastrointestinal tract to levels less likely to predispose to fungemia.

8. By "avoidance of aggravation of existing problems," I mean, for example, avoiding the development of folic acid deficiency consequent to the use of pyrimethamine in patients with bone marrow suppression from cancer chemotherapy.

As we move from these general considerations to more specific problem-solving in infection management, I would remind you not to lose sight of these points. Management of infections in immunosuppressed patients is seldom as clear-cut as it may appear to be this morning.

Pneumocystis Carinii

Pneumocystis carinii is a protozoan agent with a peculiar propensity to produce pneumonia in immunosuppressed patients, especially those with altered cell mediated immunity, and especially those in whom corticosteroids have constituted a portion of the immune-suppressive regimen.[1] It is not clear whether pneumocystosis is acquired extrinsically or the microorganisms exist in some latent form in man, to be reactivated when immunity is suppressed.

The pathophysiology of pneumocystis infection can be explained almost entirely on the basis of its location in the alveolar space where microorganisms exist in a coagulum of protein. The disease is characterized by interstitial pulmonary infiltration without pleural fluid or lymphadenopathy, and by progressive evidence of shunting with arterial blood oxygen desaturation. Tissue invasion and systemic dissemination are almost never seen. That the diagnosis is hard to establish without lung biopsy is largely owing to the location of this microorganism and the fact that it is rarely found in the sputum. There is no reliable serologic test for pneumocystosis.

The treatment of choice for pneumocystosis is pentamidine isethionate.[7] This is a diamidine drug, closely related to 2-hydroxystilbamidine (an agent sometimes employed in the treatment of North American blastomycosis). Although pentamidine has been used for 32 years in the prophylaxis and treatment of African trypanisomiasis (T. gambiense), and for 15 years in the treatment of epidemic pneumocystis infection in debilitated infants in Europe, nevertheless the drug is not commercially available in the United States. However, it can be obtained through the Parasitic Disease Drug Service at the Center for Disease Control, Atlanta, Georgia, with a minimum of delay.

The mechanism of action of pentamidine is not clear, but may be related to nucleoprotein denaturation or interference with aerobic glycolysis, or both. The efficacy of the drug in treating epidemic pneumocystosis in infants is unquestioned, most studies reporting a lowering in mortality rate from 50 percent to less than 5 percent. In immune-suppressed adults, pentamidine appears to lower mortality from 100 percent to around 50 percent.[7]

Pentamidine is usually administered intramuscularly in a single daily dose of 4 mg per kg of body weight and the recommended duration of therapy is 12 to 14 days. Serum levels of 0.3 to 0.5 μg per ml are present throughout the day so long as renal function is intact.[8] However, serum levels up to 1.4 μg per ml have been recorded in patients with severe impairment of renal function.

Table 2 shows the distribution of the drug in various mouse organs 24 and 72 hours after intraperitoneal injection in a dose of 10 mg per kg. The degree of binding to kidney and liver is impressive. The nature of the binding is uncertain, but the fact that binding occurs is probably related to the tendency of pentamidine to be slowly excreted in the urine and feces over periods of six to eight weeks following termination of therapy.

TABLE 2.—*Distribution and Level of Pentamidine in Various Mouse Organs at 24 and 72 Hours After 10 mg per Kilogram of Pentamidine Intraperitoneally*

	μg/gram in tissue	
Organ	*24 hr.*	*72 hr.*
Kidney	52	20
Liver	28	10
Spleen	11	3
Remainder of abdominal and pelvic organs	8	2
Lung	5	4
Remainder of carcass	3	2
Brain	<0.3*	<0.2

*The symbol (<) means a small fluorescence reading was obtained but no fluorescence peak or curve characteristic for pentamidine (from reference 8).

When pentamidine is given intramuscularly in man, there is a distinct tendency to form sterile abscesses at the point of injection. When the drug must be given intravenously, hypoglycemia may occur.[7] Indeed, the diamidines were originally developed as hypoglycemic agents. Pentamidine does have some tendency to produce azotemia, and its renal binding may be important in this regard. This raises a particular concern in renal transplant recipients, but to my knowledge no renal graft has been lost as a result of the use of pentamidine. There are currently no recommendations for alterations in dosage in the face of renal or hepatic disease, but hepatic and renal function should obviously be closely observed as the drug is used.

An alternative form of treatment for pneumocystosis is pyrimethamine plus a sulfonamide[9] (see below).

Toxoplasma Gondii

Toxoplasma gondii is a common pathogen in man. Disease can be acquired by ingesting poorly cooked meat which contains viable cysts or through contact with the feces of cats which have killed and eaten infected wild birds or rodents. Infants can become infected transplacentally. Probably the majority of cases of toxoplasmosis are subclinical or dismissed as "viral illness." In some instances the disease resembles infectious mononucleosis or lymphoma. Following infection, toxoplasma cysts are deposited throughout the body, including muscle and brain.[10] In immune-suppressed patients, disease probably develops when previously encysted microorganisms are aroused from latency by impairment of cell mediated immunity. Toxoplasma pneumonitis, myocarditis, and encephalitis are especially common in the immune-suppressed patient.[3]

When the diagnosis is established, often through demonstration of elevated Sabin-Feldman dye test titers and tissue biopsy, the treatment of choice is pyrimethamine with a sulfonamide.[11] This drug combination is one of particular interest from the point of view of the clinical pharmacologist, for it takes advantage of the principle that the introduction of sequential metabolic blocks in a vital biochemical pathway produces an almost inescapable lethal effect.[12] The mode of action of the sulfonamides is well known, involving a block in the formation of dihydrofolic acid from para-aminobenzoic acid (PABA). Since man does not synthesize dihydrofolate from PABA, but instead directly reduces dietary folic acid to dihydrofolate, he suffers no metabolic insult from the use of sulfonamides. However, both man and microorganism enzymatically reduce dihydrofolate to tetrahydrofolate through the enzyme dihydrofolate reductase. The ultimate product is folinic acid, a metabolically active form of folate.

A variety of drugs, most notably pyrimethamine and trimethoprim, inhibit the activity of dihydrofolate reductase and hence block the production of tetrahydrofolate and folinic acid.[13] The usefulness of these drugs resides in their greater selectivity for the dihydrofolate reductase of microorganisms as opposed to that of humans. Trimethoprim is a powerful and specific inhibitor of bacterial dihydrofolate reductase, while pyrimethamine may be more specific for protozoa, including toxoplasma and malaria organisms.[12] We do not have enough data to allow a decision as to whether pyrimethamine can be replaced by the currently popular trimethoprim in the treatment of toxoplasmosis.

Sulfonamides are administered in a dosage of 75 mg per kg per day in four equal doses. Trisulfapyrimidines are the preferred form of drug. Determination of serum sulfonamide levels is indicated in order to assure the presence of therapeutic blood levels of the drug—something on the order of 12 to 15 mg per 100 ml. Serum level monitoring is also important in order to avoid excessive serum sulfonamide levels. Dr. Robert Lehrer of this institution has recently shown that sulfonamides possess the capability of interfering with polymorphonuclear leukocyte fungicidal and, to a lesser extent, bactericidal function, especially when present in high levels (levels which are readily achievable in the serum of patients with renal function impairment).[14] The mechanism is related to inhibition of myeloperoxidase-mediated microbicidal pathways in the leukocyte. The importance of any such leukocyte defect would obviously be magnified in the immunosuppressed host.

Pyrimethamine (Daraprim®) is administered orally in a dose of 0.5 mg per kg of body weight per day in two divided doses. Some investigators recommend that the dose be doubled the first two or three days. Used in this way the drug produces a stable serum level of approximately 0.5 μg per ml. Less than 4 percent of the drug is excreted in the urine per day, and serum levels may persist for several weeks after treatment has terminated. There are currently no firm recommendations for alterations in the dosage of pyrimethamine in the face of renal failure. Sulfonamides, on the other hand, are used in reduced dosages depending on renal function and serum levels.

The major side effect of treatment with pyrimethamine is megaloblastic anemia. This can be circumvented through the prophylactic use of folinic acid or calcium leukovorin in a dose of 10 mg per day intramuscularly without interfering with the treatment of toxoplasmosis.

Nocardia Asteroides

Although I do not plan to discuss nocardiosis in detail today, I would like to point out that Nocardia asteroides may be an important cause of pulmonary and cerebral abscesses in immunosuppressed patients. The treatment of choice is a sulfonamide, generally trisulfapyrimidines, in the same doses and with the same precautions that we have already discussed.[15] There is no evidence pro or con regarding the usefulness of dihydrofolate reductase inhibitors in treating nocardiosis.

Candidiasis and Cryptococcosis

Amphotericin B

Amphotericin B has been the standard of therapy for disseminated mycotic infections for nearly 15 years. Of the opportunistic fungal infections common to man, candidiasis and cryptococcosis usually respond well, while aspergillosis and mucormycosis are more refractory to treatment. Amphotericin B is a polyene antibiotic and its mechanism of action involves binding to yeast cell membrane with subsequent loss of selective permeability of the fungus.[16] Ergosterol and dihydroergosterol are the principal membrane sterols of yeast phase fungi and are probably the predominant site of attachment of amphotericin B.

When amphotericin B is infused intravenously in doses of 20 to 30 mg or more, a peak serum level of 1.56 μg per ml is achieved which is ordinarily not affected by further increases in dosage or by alterations in renal function.[17,18] Very little drug is excreted by the kidney—only 2 to 5 percent of a given daily dose.[17] If amphotericin serum levels are followed very carefully after termination of a given course of therapy, the drug can be found for some time after the completion of treatment (Figure 1).[19] These data suggest that amphotericin is bound in some form in the body and then slowly released. Sterols of human cell membranes and cholesterol have been proposed as sites of binding. Further, since amphotericin becomes particulate in the presence of serum, it has been suggested that the drug is cleared by the reticuloendothelial system.

Whatever method the body utilizes to store this drug, the point is that serum levels provide only limited information relative to the fate of the drug in the tissues. The result is that amphotericin therapy is relatively empiric, toxicity playing an important role in deciding how therapy is to be administered. One thing we have learned, however, is that amphotericin need not be given in maximally tolerated doses in order to yield optimal therapeutic response.[18] This applies to the immune-suppressed host as much as to one who is immune-competent. In ordinary circumstances we employ sufficient daily amphotericin B to produce a serum level twice the minimal inhibitory concentration for the infecting fungus.[18] However, in exceptional circumstances we have used extraordinarily low daily dosages of amphotericin with excellent response. We have successfully treated one renal transplant recipient with tenuous renal function and Candida albicans meningitis (a chronic indolent disease) with 10 mg of amphotericin a day. Her disease was surprisingly easy to manage with this regimen, and she was treated largely as an outpatient. Intrathecal therapy was not used.

Because amphotericin is famous for its toxic potential,[20] it is especially worthwhile to review the toxic aspects of this drug as they might affect the management of the compromised host.

Immediate constitutional toxicity in the form of headache, chills, fever, anorexia, nausea, and vomiting can be minimized by avoiding abrupt increases in dosage, too low an infusion volume of 5 percent dextrose in water (D5W), or too rapid administration. Optimally the drug should be diluted in 500 to 1,000 ml of D5W and infused over a period of about six hours. Premedication with analgesics is often helpful. Thrombophlebitis is a real problem with amphotericin, and we deal with it by employing scalp vein sets and regularly rotat-

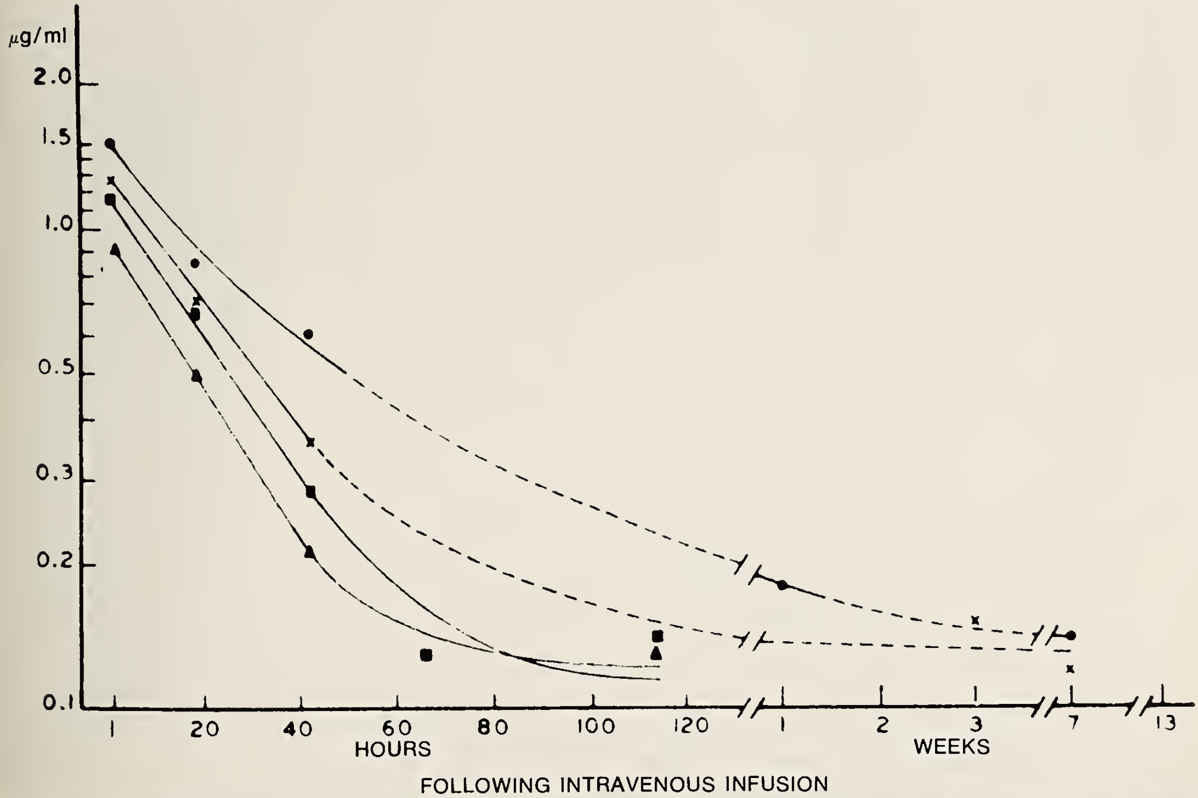


Figure 1.—Disappearance of amphotericin B from serum after completion of intravenous infusion in four patients. Serum concentrations are plotted logarithmically on the ordinate against time plotted on the abscissa. Curves are drawn by inspection; dashed areas represent extrapolation. (From ref. 19.)

ing the site of injection. It has been suggested that the addition of a small amount of heparin to each infusion may be beneficial.

Anemia is an inescapable consequence of amphotcricin treatment. Usually the hematocrit stabilizes in the high 20s. The mechanism involves interference with bone marrow iron utilization.

Azotemia is also unavoidable but can be kept within reasonable bounds by avoiding abrupt increases of dosage. Despite the occasional necessity for interruptions in treatment to allow renal function to improve (which it usually does, immediately) amphotericin begins to produce noticeable permanent renal damage only after three to five grams or more has been delivered. This is highly variable from patient to patient, however.[21]

Hypokalemia is probably a direct result of the distal type of renal tubular acidosis which develops in patients who receive this drug.[22] It is a particular problem in the patient who is receiving corticosteroids, since the latter drugs contribute to potassium wastage. We routinely provide potassium supplementation in amphotericin-treated patients, depending on renal functional status. Figure 2 depicts the hospital course of a patient with cryptococcal meningitis whose physician failed to pay attention to serum potassium levels during amphotericin therapy.[23] As his serum potassium dropped below 2 mEq per liter, he developed myoglobinuria, creatinuria, profound muscle weakness, and histologic evidence of rhabdomyolysis. He recovered with aggressive potassium supplementation.

5-fluorocytosine

A new oral antifungal agent, 5-fluorocytosine (5-FC), has considerable activity against candida species and Cryptococcus neoformans.[24] It has a structure remarkably similar to that of the antitumor drug 5-fluorouracil (5-FU). In fact, 5-FC was originally developed as an antitumor drug, but was found to have virtually no effect on mammalian cell replication. Instead, the drug has its major effect on fungi. The reason for this difference may be related to the inability of cytosine to enter the mammalian cell. In susceptible fungi

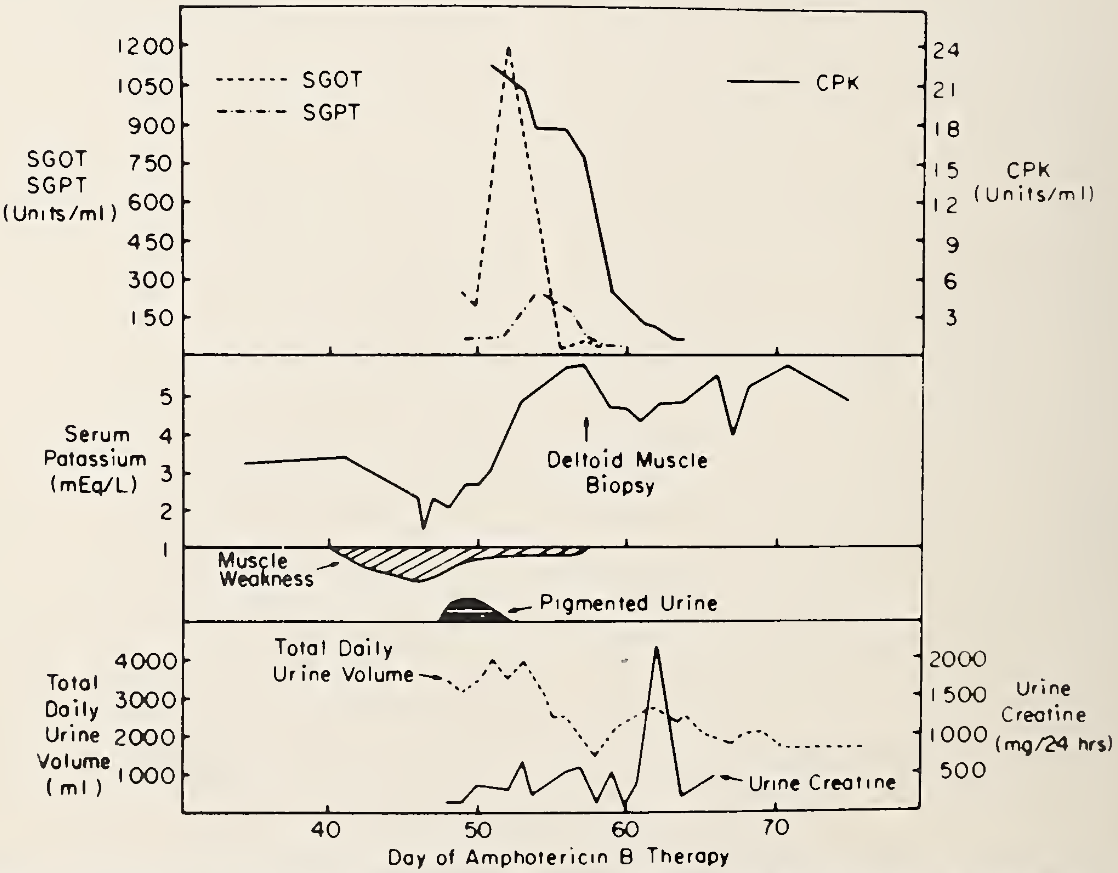
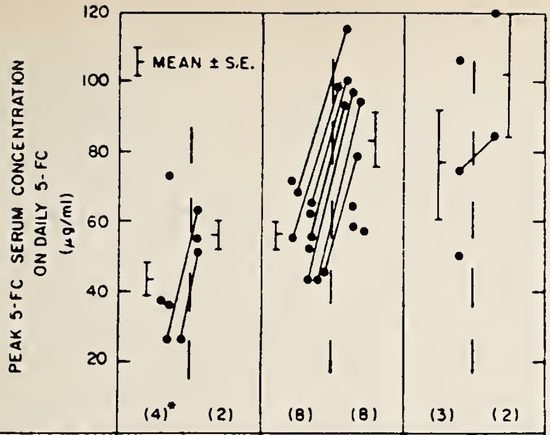


Figure 2.—Laboratory test values and clinical course by day of treatment with amphotericin B in a patient who developed severe hypokalemia. (From ref. 23.)



CREATININE (mg %)	<1.2	1.4-3.0	<1.2	1.2-3.0	<1.2	1.4-2.2
DAILY DOSE OF 5-FC	47-54 mg/kg		63-104 mg/kg		140-155 mg/kg	

Figure 3.—Effect of renal function on peak serum concentrations of 5-FC on three different dosage schedules. Solid lines connect determinations done on the same patient on a given 5-FC dosage before and after amphotericin B-induced renal insufficiency. (From ref. 27.)

5-FC is immediately de-aminated to 5-FU.[25] In essence, the administration of 5-FC is a means of delivering 5-FU to fungi without an effect on mammalian cells.

Because it can be given by mouth, 5-FC is a highly attractive drug. It is extremely well absorbed from the gastrointestinal tract and is excreted largely by the kidney in active form. Although 5-FC has been converted to 5-FU by the gut flora of rats, apparently this does not occur in man. The drug has only three important toxic manifestations: Gastrointestinal distress, liver function abnormalities, and bone marrow suppression when excessive serum levels are attained.[26]

Peak serum levels in the range of 100 μg per ml can be achieved when maximal doses of 150 mg per kg per day are employed.[27] There is excellent penetration into cerebrospinal fluid[28] and joint spaces.[29,30] Most species of candida and cryptococci which are sensitive to 5-FC are inhibited by less than 4 μg per ml of the drug.[31] Serum levels of 5-FC are not only dose-dependent but also tend to rise as renal function deteriorates.[27] One of the causes of declining renal function may be amphotericin B, a drug often used with 5-FC for potential synergistic effect.[32] Figure 3 shows serum levels of 5-FC before and after amphotericin B has produced renal insufficiency. It is clear that amphotericin strongly influences the bloodstream clearance of 5-FC. For maximal safety, 5-FC serum levels should always be monitored when 5-FC therapy is combined with amphotericin B. The measurement of 5-fluorocytosine serum levels may be especially difficult in the presence of amphotericin B and the assistance of a skilled bacteriology laboratory is critical in this regard.[27,33]

Although 5-FC appears to be quite useful in the treatment of candidiasis, only about 50 percent of candida species are sensitive *in vitro;* sensitivity cannot be simply assumed.[28] There is mounting evidence that 5-FC may be particularly useful in the treatment of renal candidiasis since extremely high levels of drug are excreted in the urine.[34] Our experience in treating fungal infections of the urinary tract with 5-FC has been favorable, but other investigators have been less impressed with this drug in similar circumstances.[26]

The only other commonly encountered fungal infection amenable to 5-FC therapy is cryptococcosis. A problem here, however, is the development of 5-FC resistance during the course of treatment.[28] A rule of thumb is that although nearly 100 percent of cryptococci are sensitive to 5-FC at the outset, nearly 50 percent will rapidly develop resistance during therapy. To counteract this tendency it has been suggested that a high dosage regimen in the range of 150 mg per kg per day be employed at the outset in treating cryptococcosis.[24]

In summary, then, 5-FC shows great promise for candidiasis, especially renal candidiasis, and may be a useful second-line drug for cryptococcosis if used in adequate dosage. The drug may find particular usefulness when employed in combination with amphotericin B. Serum level monitoring is important to avoid possible marrow suppression, and serum levels in excess of 100 μg per ml should probably be avoided.

Clotrimazole (Bay b 5097)

Clotrimazole will not be familiar to many in this audience, with the possible exception of those who have employed the drug locally in treating the lesions of the immunologic syndrome of chronic mucocutaneous candidiasis. Clotrimazole was originally highly touted in the German literature as having a broad antifungal spectrum, which included candida and aspergillus species.[35] It is now likely that this drug may be a major disappointment in the treatment of mycotic infection despite excellent credentials *in vitro*. The reason is a fascinating one, and one that should be amenable to pharmacologic manipulation.

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*The number of patients is given in parentheses.

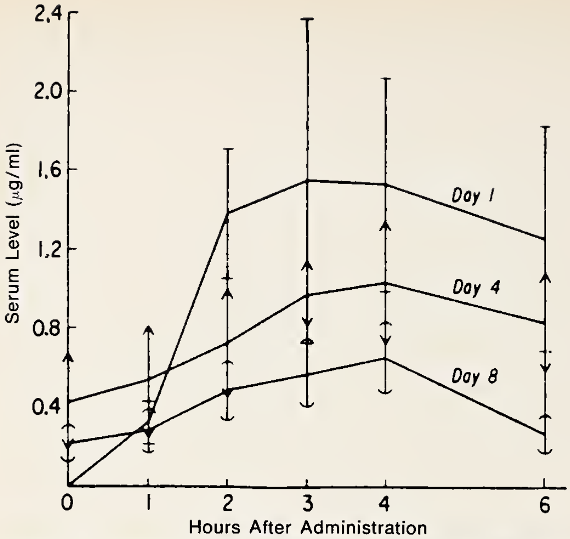

Figure 4.—Mean drug concentrations in serum after the first dose on days 1, 4, and 8 in six patients taking 1.5 gram of clotrimazole every six hours. (From ref. 35.)

TABLE 3.—*In-Vitro Activity of Carbenicillin and Ampicillin Against Selected Bacterial Species*

	Minimal Inhibitory Concentration (μg/ml)	
	Carbenicillin	*Ampicillin*
Proteus vulgaris	25.00	100.00
Proteus mirabilis	3.12	3.12
Proteus morganii	6.25	200.00
Proteus rettgeri	0.78	25.00
Pseudomonas aeruginosa (pyocyanea)	125.00	500.00
Escherichia coli	12.50	6.25
Pasteurella multocida	0.39	0.19
Enterobacter aerogenes	50.00	100.00
Klebsiella pneumoniae	12.50	1.56
Salmonella typhosa	25.00	3.12
Staphylococcus aureus	1.25	0.06
Staphlococcus aureus (penicillinase producer)	50.00	100.00
Streptococcus pyogenes —group A	0.15	0.008
Diplococcus pneumoniae	0.15	0.008

(From J Infect Dis 122 (supplement): S3, Sep 1970)

The problem is illustrated in Figure 4, which demonstrates a progressive fall in mean clotrimazole serum levels with duration of treatment. What appears to be occurring is hepatic microsomal enzyme induction with progressively rapid drug inactivation. This problem, coupled with one of erratic absorption from the gastrointestinal tract, appears to bode ill for the further development of this drug. Nevertheless, some investigators feel that it has been helpful in managing the superficial candida infections which characterize chronic mucocutaneous candidiasis. It is likely that for the time being the usefulness of this drug will be limited to the topical preparation.

Suspected Gram-Negative Sepsis

For the remaining time I would like to consider with you the extremely popular regimen of carbenicillin plus gentamicin which has evolved for the treatment of suspected Gram-negative sepsis—and especially pseudomonas sepsis—in the profoundly leukopenic, immunosuppressed patient. Obviously we could talk about every known antimicrobial agent and relate it to the compromised host. Carbenicillin and gentamicin deserve special mention because of a mystique that has developed relative to their use. It is therefore important that we understand clearly what these drugs can and cannot do.

Carbenicillin is a drug chemically quite similar to ampicillin. What makes it unique is its broadened antibacterial spectrum, extending not only to Proteus mirabilis (which ampicillin does reach) but also to indole positive strains of proteus and to Pseudomonas aerugenosa—which ampicillin does not reach (Table 3). Let me emphasize at the outset that carbenicillin has no place in the treatment of infections due to penicillinase-producing staphylococci. Penicillinase inactivates carbenicillin as surely as it does penicillin G.

Why do we consider Pseudomonas aerugenosa to be sensitive to carbenicillin when many strains require up to 125 μg per ml for inhibition *in vitro*? What are the factors which allow the attainment of such extraordinary serum levels? The reason is shown in Figure 5. If carbenicillin is continuously infused in a dose of 1 gram per hour, serum levels of nearly 150 μg per ml can be achieved. To accomplish this, however, extraordinary daily doses on the order of 24 to 30 grams must be administered. Apparently one of the major reasons that carbenicillin can achieve such extraordinary serum levels is related to the relative slowness with which it is cleared by the kidney.

Since carbenicillin can produce such high serum levels it would seem to be ideal for the treatment of pseudomonas and proteus sepsis, especially since the mechanism of action of the drug (inhibition of cell wall synthesis) should result in a distinct bactericidal effect. The problem with this reasoning is illustrated in Table 4 which demonstrates the tendency for Pseudomonas aerugenosa to become resistant to carbenicillin during the course of therapy. The mechanism of resistance involves the selecting-out of microorganisms with

TABLE 4.—*Minimal Inhibitory Concentration (MIC) of Carbenicillin for Species of Pseudomonas Aerugenosa Isolated Before and After Treatment with Carbenicillin*

MIC µg/ml	*Pretreatment Isolates*	*Posttreatment Isolates*
3.9	1	0
7.8	4	2
15.6	5	0
31.2	12	0
62.5	3	0
125.0	0	2
250.0	0	2
500.0	0	3
>500.0	0	2
TOTAL	25	11

(From Ann Int Med 73:165-171, 1970)

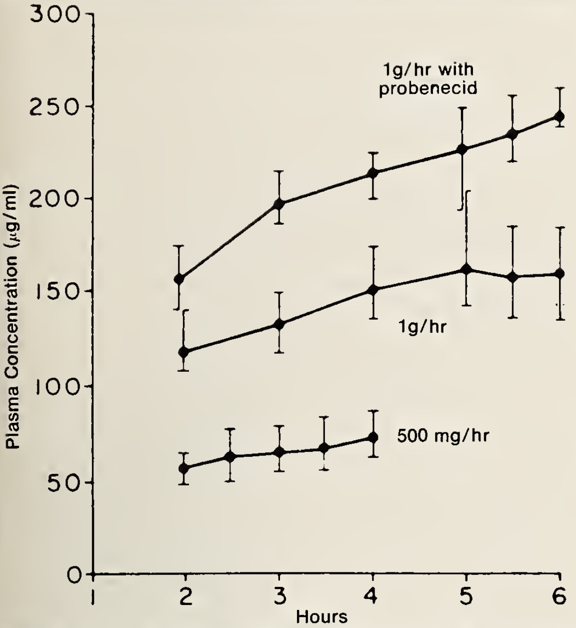

Figure 5.—Average concentrations of carbenicillin in the plasma of four healthy volunteers given a continuous intravenous infusion. (From J Infect Dis 122 suppl:510-513, 1970.)

high intrinsic carbenicillin resistance. Before treatment, 20 of 25 strains were sensitive to between 15.6 and 62.5 µg of carbenicillin per ml. Eleven strains became resistant during therapy, the minimal sensitive levels of seven rising far above those drug levels clinically achievable with carbenicillin.

What all this boils down to is that carbenicillin alone is not sufficient therapy for pseudomonas sepsis because serum levels, although high, are not high enough to prevent selection of resistant strains. Urine levels, however, are extraordinarily high since the drug is primarily excreted in the urine.[36] Therefore, the primary role for carbenicillin, when used alone, may be in treating pseudomonas or proteus urinary tract infections. It should be noted, however, that not all investigators agree with this position. Bodey and his co-workers feel that carbenicillin alone may constitute adequate therapy for pseudomonas and proteus blood-stream infections in granulocytopenic patients.[37,38]

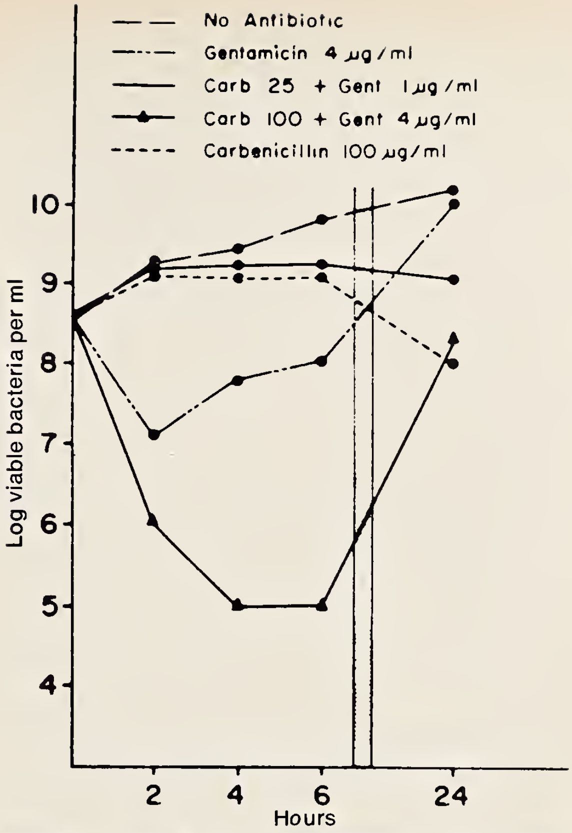

Figure 6.—Rate of killing of a resistant strain of Pseudomonas aerugenosa by gentamicin and carbenicillin, alone and in combination. 100 µg per ml of carbenicillin together with 4 µg per ml of gentamicin produced a 4 log drop in the concentration of Pseudomonas aerugenosa by six hours. The increase of bacteria to the baseline concentration at 24 hours reflects the extreme resistance of this particular microorganism to antimicrobial therapy. After all the sensitive cells were killed, the resistant organisms grew to maximal numbers. (From J Infect Dis 122 suppl:590-593, 1970.)

Gentamicin is an aminoglycoside antibiotic with an extremely broad antibacterial spectrum against aerobic Gram-negative rods including Pseudomonas aerugenosa. The antibiotic is also effective against Staphylococcus aureus. Very early, evidence was sought which would support the use of carbenicillin together with gentamicin in the treatment of pseudomonas sepsis. At first it was reported that the drugs were antagonistic. However, antagonism is likely to occur only if the two drugs are mixed in the same bottle—a very poor practice under any circumstance.[39]

Figure 6 demonstrates the more typical synergism of carbenicillin and gentamicin for Ps. aerugenosa. Neither gentamicin alone at a level of 4 μg per ml or carbenicillin alone at a level of 100 μg per ml was impressively active against this highly resistant strain of Pseudomonas aerugenosa. When used simultaneously in full dosage, however, synergism is apparent. In essence one hopes for such synergism in the blind treatment of suspected pseudomonas sepsis.

I would now like to make one final point about gentamicin. This drug was withheld from the United States market for years because of fear of nephrotoxicity. When it was released, regimens of 1 to 3 mg per kg of body weight per day were suggested, caution being the byword. Translated to dosages, this usually meant that patients received 40 to 80 mg every eight hours. Most patients receiving 3 mg per kg per day achieved peak serum levels of only 4 μg per ml. This is adequate for most Gram-negative rods which are sensitive to gentamicin, but barely adequate for Pseudomonas aerugenosa, which has a mean minimal inhibitory concentration of around 4 μg per ml. Current recommendations, therefore, stress the use of gentamicin in much higher initial doses—at least 5 mg per kg of body weight per day (or 100 mg every eight hours).[40] In these circumstances serum levels closer to 8 μg per ml will be achieved. Some investigators have employed doses of 6 to 8.5 mg per kg per day without the development of serious ototoxicity or nephrotoxicity.[41]

While caution is still indicated in the use of gentamicin, the therapeutic index being relatively low, the employment of these higher dosages is clearly indicated in life-threatening suspected pseudomonas sepsis. Serum levels of 10 μg per ml should probably not be exceeded lest damage be done to the kidneys and vestibular apparatus. Since gentamicin levels are greatly affected by renal function status, repetitive serum level monitoring is essential in the proper management of patients with pseudomonas sepsis.

In summary, it can be said that at present the combination of carbenicillin and gentamicin, administered in full dosage, does appear to be useful in the management of the immune-suppressed patient with suspected Gram-negative sepsis.[41] In most cases of proven pseudomonas sepsis the combination is clinically superior to either of the drugs used alone. In the event that some other infecting microorganism is identified, treatment can be appropriately modified. However, the usefulness of carbenicillin and gentamicin in combination lies in the apparent ability (through the broadness of the combined antimicrobial spectrum) to "buy time" in the severely immunosuppressed patient with Gram-negative sepsis.

Trade and Generic Names of Drugs

Daraprim®	pyrimethamine

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MALARIA PROPHYLAXIS AND DIAGNOSIS

Once again two Californians have returned from an African adventure with more than they bargained for—falciparum malaria. Despite delayed diagnosis, these patients survived, but their story could have been quite different since falciparum malaria is the only malaria that regularly kills otherwise healthy persons. Death or irreversible disease can occur within 24 hours of symptoms.

Malaria is preventable. Every patient preparing to visit a malarious area should receive a prescription for and a strong admonition to take chloroquine phosphate as chemoprophylaxis. The adult dose is 500 mg (300 mg base) once a week. Medication should be begun, when possible, two weeks before departure, to instill the habit pattern of drug-taking in the patient and to ensure that any toxicity attributed to chloroquine can be evaluated by the prescribing physician. (In this dosage chloroquine rarely causes untoward effects, but may occasionally precipitate vomiting, pruritis or headache.) Weekly chloroquine should be continued for six weeks after leaving the endemic area. This regimen suppresses all chloroquine-sensitive forms of malaria, preventing a clinical attack of malaria in almost all patients. When "breakthrough" malaria does occur, the clinical picture is usually mild and the response to therapy prompt.

Quartan or vivax infection may first appear weeks or months after chloroquine is discontinued as this drug has no effect on the pre-erythrocytic and exo-erythrocytic cycle. For this reason some physicians prefer to give a two-week course of primaquine (15 mg every day) to returned travelers. However, it should be noted that this regimen does not result in a radical cure of all strains of malaria which have a secondary erythrocytic cycle; failures are most notable with vivax infection acquired in the Souh Pacific.

Malignant (falciparum) malaria rarely if ever follows correct utilization of chloroquine prophylaxis unless the patient has been exposed to chloroquine-resistant strains. Chloroquine resistance is documented only for falciparum malaria. This problem is largely limited to Southeast Asia and parts of South America. Persons planning travel to these areas should be advised individually about chemoprophylaxis. The most benign regimen is chloroquine as above plus primaquine 45 mg once weekly. Other currently proposed regimens for prophylaxis of chloroquine resistant malaria offer greater protection but have some risk of serious side-effects: drugs which have been used successfully include sulfones (DFD, DDS), long-acting (sulfonmethoxine) and short-acting (sulfadiazine) sulfonamides. Prophylactic effect can be demonstrated when these drugs are given singly, but best results have been achieved in combination with pyrimethamine or chloroquine.

Difficulties occur when patients do not receive adequate and convincing advice from their physicians about chemoprophylaxis and either do not receive any medications or do not take them. Because travel to almost all malarious areas requires some form of immunization (and therefore some medical advice), these patients represent a failure of the medical profession to recognize the pathogenic potential of malaria. Having missed the first opportunity, that of disease prevention, a second source of potential difficulty is the failure to consider the diagnosis in returned travelers, either because the physician does not think of the possibility and therefore does not ask, "Where have you been?" or because the physician assumes, incorrectly, that the history of chemoprophylaxis completely eliminates the possibility of malaria. Ironically, falciparum malaria, with its attendant risk, is the type of malaria least likely to be detected on routine blood smear—the small size of the ring forms and the usual absence of larger later stages of parasites from the peripheral blood make the diagnosis easy to miss unless a specific search for parasites is instituted. With increasing numbers of peripatetic patients, physicians must step up their advice to travelers with regard to chemoprophylaxis and their index of suspicion in the febrile traveler returned.

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This informational essay was prepared at the behest of the Advisory Panel to the Section on Preventive Medicine and Public Health.

Important Advances in Clinical Medicine

Epitomes of Progress—Obstetrics and Gynecology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Obstetrics and Gynecology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Obstetrics and Gynecology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Obstetrics and Gynecology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

The Hirsute Patient

ALTHOUGH HIRSUTISM in the majority of women has a genetic basis, any sudden change in the quantity or distribution of hair at times other than puberty, pregnancy or menopause is abnormal and should be carefully investigated. Hirsutism accompanied by signs of virilization or defeminization usually is of endocrinologic origin. Determination of urinary 17-ketosteroid (KS) excretion and serum testosterone should be performed in these patients. Only if elevated levels of 17-KS—greater than 25 mg in 24 hours—are found should an adrenal source be suspected. If 17-KS are elevated, urinary pregnaetriol should be measured to rule out adult onset of congenital adrenal hyperplasia. An overnight dexamethasone suppression test (1 mg taken orally at 11 PM followed by an 8 AM serum cortisol determination) can rule out Cushing's disease or an adrenal tumor if the cortisol is less than 5 μg per 100 ml. The most common endocrinological cause for hirsutism is polycystic sclerotic ovaries. These patients almost always have 17-KS less than 25 mg per 24 hours, elevated serum LH, normal serum FSH and only slightly or moderately elevated serum testosterone. Treatment may include clomiphene citrate, gonadotrophin suppression with oral steroid contraceptives and occasionally ovarian wedge resection. If the serum testosterone is markedly elevated and 17-KS are normal, an ovarian tumor should be suspected. If catheterization of the ovarian veins shows pronounced difference between the two testosterone levels, an androgen-producing unilateral ovarian tumor is probably present. If testosterone levels are similar, a severe form of PCO is probably the cause of the hirsutism.

DANIEL R. MISHELL, JR., MD

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Clinical Application of Genetic Detection and Counseling

It is now recognized that 7 percent of all conceptuses have chromosomal errors; most are aborted. The incidence of chromosomal errors in newborns is 0.5 percent but they produce recognizable phenotypic changes in fewer than half of the cases. Quinacrine staining of chromosomes allows identification of Y chromosome not only in mitosis but in all cells. It is imperative that this technique and the rapid Giemsa banding technique be employed in all chromosome studies. It allows specific identification of all elements and detects rearrangements not visible before. Its application is important in evaluation of habitual aborters (6 to 10 percent of husbands or wives are abnormal), of unexplained infertility patients, and of repeated congenital anomalies. In my opinion all semen donors should be karyotyped. Amniotic fluid analysis is now successful in 95 percent between 14 and 16 weeks of gestation. Numerous centers will assist in analysis and counseling for chromosomal and genetic errors.

Kurt Benirschke, MD

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Important Advances in Paracervical Block Anesthesia

Should paracervical block (PCB) anesthesia be banned? Recently, the Food and Drug Administration considered and then decided against this extreme action. Despite a growing number of reports regarding the fetal hazards of paracervical block, this easily administered anesthetic remains popular and often useful.

Fetal bradycardia is the most common complication, occurring in 20 to 30 percent of patients. Bradycardia usually develops within 2 to 10 minutes and lasts from 3 to 20 minutes. When bradycardia occurs, fetal acidosis and high fetal blood levels of local anesthetics are found. Increased uterine activity has also been reported by some authors.

There is evidence that local anesthetics are the direct cause of bradycardia:

1. Local anesthetics administered intravenously to the mother can produce fetal bradycardia with no accompanying maternal hypotension or acid-base changes.
2. Increasing the dosage of local anesthetic can increase the likelihood and severity of bradycardia.
3. Using a less toxic local anesthetic (propitocaine) can result in a lower incidence and shorter period of fetal bradycardia.

We have postulated that in 20 to 30 percent of patients undergoing PCB, local anesthetic reaches the fetus in unusually high concentrations via diffusion across the uterine arterial walls. This results in transient fetal bradycardia, decreased cardiac output, hypoxia and metabolic acidosis. On the other hand, some investigators have questioned this etiologic postulation for bradycardia and acidosis. They have found that local anesthetics, when injected directly into the (human anencephalic) fetus in huge amounts, do not produce fetal bradycardia nor the same EKG changes as those found during PCB-bradycardia. Fetal EKG changes during PCB-bradycardia are very similar to those found during fetal asphyxia. Consequently, those workers postulate that the local anesthetic compromises uterine blood flow, either directly by uterine vasoconstriction or indirectly by uterine muscle hyperactivity which results in fetal hypoxia and bradycardia.

While the precise cause of fetal bradycardia may be controversial, the significance is not. PCB-bradycardia indicates fetal distress. Increased neonatal morbidity and indeed mortality occurs when bradycardia follows PCB. Currently, American and European medical journals contain reports of 50 perinatal deaths associated with PCB.

Because of the potential fetal and neonatal hazards of PCB, we believe that this technique should not be used in cases of utero-placental insufficiency or prematurity or where there is pre-existing fetal distress. There may be exceptions if other anesthetic techniques are contraindicated or pose a greater hazard to the mother or fetus.

When the technique is used, drug dosage must be kept to a minimum. The fetal heart rate should be carefully monitored for 30 minutes after PCB. One must be prepared to treat neonatal depression with oxygen, positive pressure ventilation, and bicarbonate administration if fetal bradycardia develops after the block.

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Sol M. Shnider, MD

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Genetic Counseling

ALTHOUGH TREATMENT of genetic disorders is making progress, many of these diseases are still untreatable and successful management lies in prevention. In this, genetic counseling plays a significant role by establishing the risk of a disorder to occur or recur in a family and in giving a couple the choice of whether they wish to take that risk for having an affected child. Optimum genetic counseling requires an accurate diagnosis, a complete accurate family history (pedigree), a good fundamental knowledge of genetic principles, and a familiarity with the latest literature concerned with the disorder in question.

Genetic counseling is based on the Mendelian laws of inheritance for single gene problems, and on empirical recurrence risks for polygenic and multifactorial traits. Some diseases, such as the Marfan syndrome, are inherited in an autosomal dominant fashion with each affected person having a 50 percent risk for having an affected child with each pregnancy. Other disorders, such as some inborn errors of metabolism (phenylketonuria and galactosemia, for example, are inherited in an autosomal recessive manner with each parent being a carrier of the mutant gene; each pregnancy of such a couple has a 25 percent risk of being homozygous for the mutant gene and having the disorder. Most sex-linked (X-linked) disorders, such as hemophilia, are recessive in nature and manifest almost exclusively in males, with females being carriers who have a 25 percent chance of transmitting the gene to any offspring. However, because females have two X chomosomes and males only one X chromosome, almost no female offspring are affected while 50 percent of the males are affected.

Empirical recurrence risks are available for traits in which many different genes may be responsible (polygenic) or in which environmental factors play a significant role (multifactorial), and in the chromosome problems. Since the basic cause of the disorder is not known in most of these problems, it is not possible to predict from basic principles what the risks or recurrence risks are for a given disorder. However, by observing a large number of affected families, it is possible to determine an average risk figure. Although this approach makes certain assumptions which may not be completely accurate at the biological level, there currently is no better approach to counseling for these problems.

The recent major advance of amniocentesis for prenatal diagnosis considerably increases the accuracy of genetic counseling in some genetic problems. Amniotic fluid can be obtained at about the fourteenth week of pregnancy and examined for manifestation of a mutant gene or chromosome abnormality. Generally it is desirable to grow amniotic cells in culture to examine their chromosome and sex chromatin constitution and to search for evidence of inborn errors of metabolism. As to genetic traits that are expressed in the amniotic cells, it offers opportunity to establish whether a fetus is affected with a given disorder at essentially the 100 percent level of accuracy. This test is usually performed only if a therapeutic abortion is contemplated for a genetically defective fetus.

With the increasing trend toward limiting the size of families with the associated desire to have normal children, and because of the general desirability of utilizing preventive means in management of certain disorders, it seems likely that the importance and significance of genetic counseling for clinical practice, especially in obstetrics, will greatly increase in the near future.

ROBERT S. SPARKES, MD

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Respiratory Distress Syndrome: How It Can Be Prevented

THE RESPIRATORY DISTRESS SYNDROME can be prevented in most cesarean or elective deliveries.

With the assistance of a new test performed on the amniotic fluid of the mother, the intrauterine fetus's lung maturity can be determined quite accurately so that delivery can be performed with the least degree of morbidity for the newborn.

The "Gluck test" which determines the lecithin and sphingomyelin ratio (L/S ratio) on the aspirated amniotic fluid makes this possible.

It has been determined that when the lung tissue becomes mature, the percentage of sphingomyelin to lecithin increases markedly so that an L/S ratio of 1 to 1 means the lung is immature and delivery at that time is associated with almost 100 percent mortality of the newborn, whereas a 1 to 1.5 gives about 50 percent mortality, and a 1 to 2 gives moderate to mild symptoms in the newborn; and when the L/S ratio is above 1 to 2 the percentage of complications is markedly decreased.

The technique of aspirating amniotic fluid has been perfected to the point where it produces a very low risk to the fetus and the mother. Approximately 2 ml of amniotic fluid is needed for this test.

In all elective cesarean sections or induction deliveries for therapeutic reasons, this test should be performed before operation so that the physician can be assured that the maturity of the infant's lung is adequate to support life. If this is carried out, in almost all cases the infant can be delivered with minimal risk of the respiratory distress syndrome.

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Hypothalamic Hormones

IT IS NOW WELL KNOWN that the hypothalamus is the ultimate controller of the secretion of anterior pituitary hormones. Polypeptides of hypothalamic origin have been identified and successfully synthesized for TRF (thyrotropin-releasing factor, 1971), LRF (luteinizing hormone-releasing factor, 1972), and SRIF (somatotropin-release inhibiting factor, 1973), by Drs. R. Guillemin and A.V. Schally's laboratories. Unexpectedly, TRF not only causes pituitary release of TSH but also a prompt release of prolactin. Thus, the association of thyroid dysfunction and galactorrhea may now be explained and TRF may be considered as a specific prolactin-releasing factor. LRF induces a prompt gonadotropin secretion which is greater for LH than for FSH. It has been shown that estrogen exerts a direct influence on pituitary gonadotropic cell as evidenced by a change in LRF responses. Both TRF and LRF have provided a direct and sensitive test in distinguishing disorders of hypothalamic versus pituitary origin. Hypogonadotropic amenorrhea with normal or not infrequently exaggerated response to LRF may be assured of a functional disturbance of hypothalamus as a cause rather than pituitary neoplasm. The usefulness of LRF in the induction of ovulation and future development of blocking agents for LRF (LRF-analogs) in the conception control is promising. Most recently, a peptide hormone was synthesized which inhibits growth hormone release. Indeed, a new era of neuroendocrinology has begun with expectation that soon it will apply to clinical medicine.

S. S. C. YEN, MD

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Use of Amniotic Fluid: Assessment of the Fetus

AMNIOTIC FLUID, obtained early in the second trimester by transabdominal amniocentesis, can be used to diagnose a number of hereditary and congenital disorders in the fetus. Biochemical enzyme tests on uncultivated or cultivated cells, sex determination and karyotyping may then be performed in time to consider therapeutic abortion.

Management of the rhesus sensitized pregnancy mainly rests on the results of spectophotometric analysis of amniotic fluid. As the concentration of bilirubin in amniotic fluid reflects the severity of fetal hemolytic disease, the optical density at 450 microns is used to indicate if fetal transfusion or premature delivery is necessary.

The amniotic fluid creatinine concentration, optical density and cytologic study are all useful in determining the duration of the gestation, size of the fetus, and fetal hepatic and renal maturity. Phospholipid analysis of the fluid reflects fetal lung maturity and helps in predicting whether respiratory distress will develop in the newborn.

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Current Concepts of Fetal Monitoring

RECENT STUDIES of perinatal brain damage in fetal monkeys support the concept that "ominous" fetal heart rate (FHR) patterns may reflect fetal hypoxia and asphyxia. Such FHR patterns are difficult to detect by auscultation but are readily detected with electronic techniques.

At present, fetal monitors are used mainly for management of high-risk patients, not only to record FHR patterns but also to provide an accurate assessment of uterine contractions. The importance of the latter as a repetitive stress to the fetus is now being recognized.

Clinical experience with fetal monitoring having suggested that it is of benefit to the high-risk fetus, serious consideration is being given to the advisability of monitoring all patients in labor in order to decrease the birth hazards for uncomplicated as well as complicated pregnancy.

EDWARD H. HON, MD

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Serum FSH-LH Determinations in Gynecologic Practice

THE DEVELOPMENT of radioimmunoassay for the measurement of protein hormones has made it possible to measure the small amounts of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) present in serum. Therefore, it is no longer necessary to depend upon bioassay of urinary gonadotropins. The latter methods were cumbersome because of the necessity of collecting 24-hour specimens of urine and because of the lack of sensitivity of the methods, particularly those for the measurement of LH.

Serum FSH and LH have been measured during the various phases of life such as childhood, menstruating years, and postmenopausal years. They have also been measured at frequent intervals during normal and abnormal menstrual cycles. In the latter, it has been noted that FSH and LH levels change very rapidly and dynamically, particularly at the time of ovulation: The amount of LH may double over a six-hour period and then quadruple over the ensuing six hours.

These reports make it clear that single determinations of FSH and LH are of value for the detection of some conditions. Absence of pituitary function in this sphere will be reflected by undetectable FSH and LH. Ovarian failure, for whatever reason, will be reflected by very high levels of FSH and LH.

For the evaluation of menstrual disorders such as oligomenorrhea, amenorrhea, and inadequate corpus luteum, single measurements of FSH and LH are not sufficient. In these situations the pattern of FSH and LH levels during complete cycles is essential for proper understanding. The ratio between FSH and LH may well be important in some of these conditions. Therefore it is necessary to collect daily specimens of blood for the delineation of those patterns.

Single determinations will not suffice because the levels of FSH and LH may both be well within the range of normal for a menstrual cycle and yet the complete pattern for a full cycle will differ significantly from that for a normal cycle. Patients with polycystic sclerotic ovaries may have LH levels which are chronically elevated but not outside of the range for a normal menstrual cycle. Similarly, some patients with amenorrhea will have chronically depressed levels of LH. A patient with an inadequate corpus luteum may have lower than usual levels of FSH in the early part of the cycle but still within the range noted in normal cycles.

WILLIAM J. DIGNAM, MD

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Laminaria Tents as an Aid for Suction Abortion

RAPID INSTRUMENTAL DILATATION of the cervix before suction abortion is frequently the most difficult and traumatic part of the procedure. The use of laminaria tents formed from seaweed (laminaria digitata) to accomplish this dilatation has greatly simplified the operation.

A laminaria tent is inserted without anesthesia into the cervical os so that only the tip of the tent can be seen at the external os. By hygroscopic action the tent expands from a diameter of 2 to 3 mm to 9 to 12 mm. At the time of suction curettage, 12 to 18 hours later, the laminaria tent is removed, almost always without difficulty. Suction curettage is completed in the usual fashion.

In at least two out of three cases, the cervix is dilated a minimum of 9 mm at the time of suction. Further dilatation, if needed, is almost always easily accomplished. Complications have been few. The rare impaction of the tent in the cervix can apparently be treated by careful mechanical dilatation of the cervix adjacent to the tent, thus allowing its removal. The risk of infection does not seem to be increased by the use of the tent. Use of the tent has permitted us to accomplish abortion in almost all instances without general anesthesia and without significant discomfort to the patient.

Kenneth Niswander, MD

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Vaginal Adenosis

Vaginal adenosis (submucosal glands lined by mullerian-type epithelium) was rarely described in the past. It has been seen frequently in young women whose mothers took diethylstilbestrol and similar compounds during pregnancy. The adenosis can appear as a red granular lesion. Biopsy of these red areas as well as those that initially appear normal but fail to stain with Schiller's iodine can usually be accomplished in the office. Although these glands appear to be benign, they have been observed in close proximity to clear-cell adenocarcinomas that have also occurred in young females whose mothers took stilbestrol during pregnancy. Present estimates suggest that the carcinomas are rare among the exposed population while adenosis occurs frequently. Although adenosis has been treated by surgical excision and local destruction (cauterization), the natural history of stilbestrol-associated adenosis is unknown. Close follow-up of patients with vaginal adenosis is certainly indicated and in many instances might prove to be the most prudent approach.

Arthur L. Herbst, MD

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Herpes Genitalis

Herpes genitalis is a common venereal disease, caused most usually by herpes simplex virus (HSV) type 2, which occasionally results in neonatal herpes and may be causally related to cervical cancer. Although often subclinical, primary cases, occurring in persons with no HSV antibodies, tend to be more severe clinically than recurrent cases.

In females, the cervix is most commonly involved, and the vulva, vagina and perineal areas can also be affected. In males, vesticles or ulcers can be noted on the penis, scrotum or adjoining skin areas and the virus can be isolated from the urethra, prostrate and testicles in asymptomatic cases. In either sex, HSV-2 can also involve the anus or mouth. Complications of genital herpes include neuralgia, meningitis and myelitis. In diagnosis it is most often confused with other venereal diseases, particularly chancroid, but can be confirmed by virological or cytological methods.

Because of the association with cervical cancer, infected women should have frequent Papanicolaou screening tests; and because of risk to the newborn, abdominal delivery should be considered if the genital infection is noted around the time of delivery. Since topical antiviral agents do not appear to be beneficial, treatment is symptomatic. However, three new approaches are currently under evaluation: (a) photodynamic inactivation; (b) HSV-2 vaccines, currently available only in Europe; (c) use of systemic antiviral drugs, reserved so far for the immunosuppressed patient with severe lesions.

Andre J. Nahmias, MD

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Use of Estriol Levels to Permit Delivery of Frank Diabetics at Term

The use of urinary estriol determinations to monitor fetal-placental well-being in "high-risk" pregnancies has been accepted practice for a number of years. In 1965 Greene et al, among others, reported on the usefulness of estriol determinations in the management of diabetes complicated by pregnancy.

Perinatal morbidity and mortality statistics have demonstrated that the optimum time to deliver insulin requiring diabetics (White's classes B to F) is at 36 to 38 weeks of gestation. In large clinical populations incorrect estimation of fetal gestational age is the most frequent cause of prematurity, a particular hazard to the diabetic infant. Recently Goebelsmann et al have shown that pregnant diabetic women in hospital can be allowed to continue to term and spontaneous labor, provided *daily* estriol determinations do not indicate fetal jeopardy.

The prime prerequisites for such management of the frank diabetic patient are continuous stay in hospital, a reliable laboratory with daily estriol assay capabilities, continuous fetal monitoring capability and a neonatal intensive care unit.

FREDERICK W. HANSON, MD

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The Role of Colposcopy in Gynecologic Practice

CERVICAL COLPOSCOPY recently has been recognized as a valuable means of evaluating clinical abnormality of the cervix.

A reddened, raw, inflamed cervix may represent infection, an outgrowth of endocervical epithelium onto the ectocervix (ectopy), or cancer. The lesion may or may not be associated with excessive vaginal discharge or post-coital spotting. Since the presence of carcinoma is a definite possibility, steps must be taken to establish a diagnosis.

Since the early 1940's the Papanicolaou smear has been the most popular method of detecting cervical neoplasia in the United States. This screening method is limited, however, since 10 percent or more cervical lesions may be missed. Neoplastic disease which is not detected by the cervical smear may be revealed by random cervical biopsy. However, it is not possible to definitely exclude invasive carcinoma even if the biopsy reveals a preinvasive cancer, and the need for cervical conization is apparent. Since cervical conization is not without serious sequellae a procedure which decreases its necessity would be of great advantage.

In colposcopy, the 13X magnification provided by the colposcope allows easy visualization of the ectocervix. By direct visualization the non-neoplastic causes of the abnormal cervical appearance are recognized and the need for other than routine cytologic screening is eliminated. However, if colposcopic patterns of neoplasia are detected, the most abnormal areas of the ectocervix are located and biopsy specimens are taken.

When neoplasm is present, the colposcope is also used for determining, without resort to cervical conization, the treatability of the lesion. Treatment with cryosurgery or primary hysterectomy for dysplasia or carcinoma *in situ* is carried out under the following special conditions after colposcopic evaluation by an experienced colposcopist:

1. The entire area of neoplasia is present on the ectocervix;
2. A well-defined squamocolumnar junction is located near the external cervical os;
3. The possibility of endocervical extension is eliminated by a negative endocervical curettage.

When these criteria are met, invasive cancer is excluded and cervical conization is avoided in more than 85 percent of patients with abnormal Papanicoloau smears.

DONALD R. OSTERGARD, MD

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EDITORIAL

Progress in Epilepsy

> *The kind of prayer that interests the Boones most, however, is the prayer that heals. Both Pat and Shirley believe that exorcism (the ritual casting out of devils) is a much-too-neglected therapy for the mentally disturbed. "What we call fits, seizures and epilepsy today," he explained, "Jesus recognized as possession by demons. Jesus saw epilepsy for what it is—the work of Satan. And he healed by casting the devils out."*
>
> —From "Pat Boone Believes in Miracles,"
> *McCall's Magazine,* Page 122, February 1973

THE EXCELLENT REPORT ON Recent Progress in Epilepsy which appears in the pages of this issue of CALIFORNIA MEDICINE can be used as an up-to-date mini-text to great advantage. A loss of consciousness as a symptom continues to present as a frequent diagnostic challenge, and the treatment of it involves increasingly complex and changing strategies. Dr. Tharp's review should greatly assist the non-neurologist in more effectively identifying and treating the great majority of convulsive disorders.

In spite of the measured progress in improvement and enlightenment in the area of public opinion regarding epilepsy, a more than occasional expression such as the above quotation, indicates an incredible lack of understanding. The belief in demons is doubly archaic—first in that epilepsy is classed as a mental disturbance and second that it is an example of demonic possession. Though this public display of the opinion of a television and movie personality might be considered as innocuous, it is symptomatic of the need for still further efforts in education about epilepsy.

Though not appearing as a specific heading in the review, the topic of prevention of epilepsy is implied. There are two broad areas for consideration under this category—factors operating in genetic epilepsy and those of significance in acquired convulsive disorders. The hereditary aspects of seizures have not been a popular subject among groups attempting to restore epilepsy to public respectability. (It was once a sacred disease.) Evidence discussed in the review, however, would indicate that genetic factors are operative not only in "idiopathic," "centrencephalic" or "cortico-reticular" type but in febrile seizures, focal seizures, and the vulnerability for post traumatic epilepsy. One preventive tactic, then, would be the use of genetic counselling, a discipline that is developing increasing importance in the field of neurology.

An attempt to prevent acquired epilepsy should focus on the two highest contributing causes of epilepsy—the first being the physical and metabolic traumas associated with being born, and the second, the head injury of later life. Great achievements in the prevention of epilepsy would be made if prematurity could be prevented. Probably a lesser but still a definite impact would be noted if fetal monitoring techniques were not only more developed but more extensively used. Neurosurgeons are to be commended for the decline in the frequency of post-traumatic epilepsy as measured by war-time experience with head injuries. A current field of research is the effectiveness of the prophylactic use of anticonvulsants after head trauma in preventing seizure disorder.

Under the section on anticonvulsant medication in the review, a few new names appear (Tegretol® and Clonazepam®) but these do not appear to be the long awaited, all-inclusive, super seizure-stoppers which have been a part of every neurologist's fantasy. It is apparent that the progress in the pharmacological treatment of epilepsy resides in the better management of the old, rather than the introduction of the new. This increasing effective use of such stand-bys as diphenylhydantoin, phenobarbital, and primidone resulted from the technological advance in measuring blood levels of anticonvulsants.

The availability of the determination of anticonvulsants as a clinical procedure as well as more basic pharmacological research has permitted a greater degree of therapeutic effectiveness in dealing with specific patients. Blood level determinations might be expected to answer the following types of questions. Has he been taking his medication? How close is his blood anticonvulsant level to an alleged therapeutic range? If multiple agents are being used and the patient becomes toxic, which is the responsible drug? More generalized information is available, such as the half-life of the major anticonvulsant agents. Data of this type are essential for the intelligent use of a compound, as for example in strategies designed to rapidly achieve a therapeutic level with diphenylhydantoin or in determining the feasibility of administering the entire daily phenobarbital dose at one time.

The review indicates the difficulties that the clinician might experience with the use of anticonvulsant blood level determinations. These difficulties may be of different orders, ranging from problems of accuracy and reproducibility in clinical laboratories to inappropriate action based on the laboratory data. It is becoming apparent that the "therapeutic range" is quite broad, with a great deal of individual variation. This leads to the second aphorism in caring for patients with seizures: "Don't treat the laboratory slip!" (The first aphorism was, "Don't treat the EEG!")

A final warning about the use of anticonvulsant blood level determinations is that the technique can be construed by both the physician and the patient as a type of "lie-detector" test. The implication of finding low levels in the presence of reasonably *prescribed* doses is that the patient may not be taking his medication. A further inference that is dangerous is that the patient is therefore poorly motivated, unreliable, and possibly ungrateful. Gas-liquid chromatography is not a personality test.

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The Price of Quality In Medical Care

IN RECENT YEARS there have been many efforts to identify and define what is meant by quality in medical and health care. There have been studies, discussions, symposia and workshops of many kinds and under many auspices. Medical associations, schools of public health, governmental agencies and educators have all taken a crack at it. But what has so far emerged has been substantially less than what is needed. Meanwhile the costs of health care, with or without evidence of quality, have risen alarmingly and in consequence costs are beginning to displace quality as the primary concern. Somehow the price of quality must be identified lest it be lost.

The current effort to come to grips with this is to be found in the Professional Standards Review Organization (PSRO) concept which has been enacted into law. As we understand it, PSRO's are to develop standards for medical services which will presumably assure quality and also become the criteria upon which determinations of payment will be made and through which cost can be controlled. This is simple enough in concept; in fact it closely parallels the method used in both government and industry, where specifications are developed for the purchase of goods or services, usually from the lowest bidder. On the surface this sounds good. All that is necessary is to agree on some professional standards which will reflect the desired quality and then to control costs by monitoring the utilization of the services.

However, there are reasons to believe that this approach cannot succeed without sacrifice of the very essence of quality. The reasons depend on the fact that at least three of the most important elements in medical care are independent variables which defy standardization. The first of these independent variables is the art and science of medicine itself, which is always changing and improving with experience and scientific and social progress. The second is the patient or the recipient of these ever-changing and improving services. Each person who is given care is different from every other person, each has a unique genetic endowment and a unique life experience, and therefore often unique health care needs. A third element which is equally an independent variable in health care is the process by which the first two are made to interact with one another to overcome illness or improve health in a given person in a given situation. This essential process involves freedom for the physician to select the most appropriate care and services from the ever-changing and improving resources of the art and science of medicine, and the freedom of the fully informed patient to participate in decision-making with respect to his own care. Quality in medical care requires that each of these variables be separately considered in each individual practice situation, and therefore quality is lost roughly to the extent standardization takes place.

However, we are now entering a period when, by law, standardization and specification of medical services will be attempted in the name of controlling costs. Unfortunately, not only is quality likely to be compromised for the reasons stated, but costs of care will probably be increased. For one thing, no one will receive less costly care than that determined to be standard, while many will need more. This will increase costs. And for another, the apparatus to establish, monitor, enforce and perhaps change standards and specifications can only be cumbersome and additionally expensive. An enormous amount of energy and money is certain to be invested before the effects are known.

But our concern in this editorial is with the price of quality and with how quality can be strengthened in an atmosphere of growing concern with costs. It is suggested that the price of quality can be derived from the characteristics of the three fundamental but intrinsically independent variables in medical care discussed above. If this be the case, the price includes the following. First, there must be a dynamic, changing and improving art and science of medicine. This requires active support of research, education and continuing education. Second, there must be full recognition of the uniqueness of every person and all that this implies for medical care, personal health and well-being, and for social progress. This element of quality requires the active support of the concept of biologic and social individuality and the right to self-fulfillment and the responsibility to respect the rights of others in an increasingly interdependent and collectively oriented society. Third, there must be freedom in medical care, freedom to choose and to select what had best be done in a given circumstance—freedom for both patient and physician to do this. The recognition of this freedom as an element of quality in medical care imposes responsibility. There is the responsibility of assuring availability and access to the best in the science and art of medicine for both physician and patient, there is a responsibility for both physician and patient to be well-informed, and there is a responsibility of eternal vigilance without which freedom in medical care as elsewhere will certainly be lost. There cannot be quality without responsibility.

If such is the price of quality in health care, what can be done now to bring public concern with quality more nearly into balance with present concern with costs? Obviously public pressure to pay the price for quality must become at least equal to the public pressures to control costs. It is suggested that what is now needed is a vigorous and powerful advocacy of the public interest in the *nature* of quality and the *price* of quality in medical and health care. Both the nature and the price must be clearly identified and public opinion convinced that the price is necessary and worth paying. This is an opportunity for organized medicine. The foundations for such an advocacy are to be found in many existing commitments and programs. But the scope and tempo of the effort must be vastly increased until a critical mass of public opinion is aroused and then brings its enormous power to bear on improving quality as well as on controlling costs in medical care.

—MSMW

Counseling About Sickle Cell

THE ARTICLE, "Identifying and Counseling Patients with Sickle Cell Trait," by Dr. W. Byron Smith et al, which appears elsewhere in this issue, offers a good review and bibliography of screening methods with useful comments on determining appropriate target populations and the content of genetic counseling. However, the authors' comments on recent legislation require clarification. They note that the California Legislature has passed a bill dealing with sickle cell anemia. This bill, AB 2786, introduced by Assemblyman Leon

Ralph, declares that it is the "policy of the state that every effort should be made to detect sickle cell anemia" and *requires* "the Department of Public Health to designate tests and regulations to carry out policy." Major assistance in accomplishing this task was provided by Senate Concurrent Resolution 123, introduced by Senator Mervyn Dymally, which directed the "State Department of Public Health to appoint an advisory committee to investigate and make recommendations relative to the control and treatment of sickle cell anemia."

Such a report has been made to the 1972 California Legislature and is available to interested parties. Also regulations have been developed for inclusion in the California Administrative Code and are in the process of being submitted to the State Board of Health for their approval.

The process by which this report and recommendation were developed is important as an example of one method of establishing goals in a health program. Dr. Smith's article lists a source of goals for sickle cell screening programs. Presumably these represent an informed selection of recommendations from experience and the medical literature. The first two goals relate to health education: (a) regarding reproduction, and (b) regarding occupational risks. The third and fourth goals relate to the identification of diseases or potential disease states such as the homozygote SS or sickle variants, such as SC. Other goals might be considered, however.

The State Department of Public Health report to the California Legislature is based on the deliberations of a fairly large committee of professionals (many are listed in Dr. Smith's bibliography), members of the black community, representatives of interested voluntary organizations, individuals with personal experience of the health problem itself, and representatives from the California Medical Association, the California Hospital Association, the California Council of Local Health Officers, and the State Department of Education. Presumably this gives a fairly representative base to the deliberations in a reasonably efficient management context.

The goals of this report are somewhat similar to those of Dr. Smith et al. The report states, "The first priority in a program aimed at reducing the impact of sickle cell anemia lies in the area of public education." The importance of providing accurate information about the disorder and knowledge about personal health status to individuals is stressed. A second priority is the establishment of specialized treatment centers for the patient with sickle cell anemia. The third priority relates to screening. The first issue is to identify the homozygote, the patient with sickle cell anemia. Here our recommendation is to screen infants for anemia and then to identify the hemoglobin pattern in anemic infants. It was felt that screening in the newborn period for hemoglobin S, although technically possible using agar gel[1] electrophoresis, presents too many problems at this time to be recommended for a public program. Second, because of the documented risk to the individual SS or SC patient in two clinical states, namely pregnancy and general anesthesia, and the attendant challenge to clinical management, it was felt that it should be mandated on providers to offer prenatal sickle cell screening and screening at the time of hospital admission. This determination was reached in part on the basis of a survey of 521 general hospitals in California made by the State Department of Public Health in January 1972.

It was found that "the majority of hospitals did not have a policy of screening all blacks for sickle cell." Screening of all blacks on admission was a policy in only 4.5 percent of hospitals and screening before a surgical procedure was a policy in only five percent. Also it was found that the ratio of the number of sickle cell tests performed to the number of black patients admitted was only 1:3. This shows that testing for sickle cell disorder is not widespread and suggests that a specific individual's sickle cell status may remain unknown even in hospitals. Naturally, such medical information is privileged and requires prior consent of the patient. Finally, the report notes that screening for the purpose of genetic counseling should be readily available. Continuing research seeking a cure and ongoing evaluation of screening programs constitute the remaining goals.

Turning to the screening process itself, Dr. Smith et al indicate some criteria for test selection. One of these is "simplicity so that it can be performed . . . by personnel without previous laboratory training." Which test is selected will obviously determine the type of personnel required to carry it out. Much direct discussion on involvement of community people in the testing program arose in committee. It was felt that accuracy and the ability to distinguish between heterozygosity and homozygosity with regard to hemoglobins A, S, and C on the initial test should be the major criteria of test selection. Hemoglobin electrophoresis, followed (where indicated) by additional electrophoresis or a solubility dithionite test to differentiate hemoglobin s and other non-sickling hemoglobins which may have similar electrophoretic mobility as s, is currently recommended. It might be added that black members of the committee were most strong in their support of this recommendation.

In the process of screening test selection, the problems of specificity and sensitivity must be balanced. Almost any test will have some false positives and some false negatives. The cost of the false positives (anxiety, referral costs, and the like) and the cost of false negatives (non-identification) must be balanced against the benefits of the entire program. Therefore, the question of economy must not be reduced merely to the cost of the test itself.

The question of the what and how of genetic counseling arises. What should constitute the medical content of counseling with regard to sickle cell anemia is fairly clear. The question of the epidemiology of trait is more problematic. Individual case reports are difficult to evaluate, especially those involving postmortem study. Clearly, the process of dying involves the onset of a deoxygenated state. Therefore, the demonstration of sickling, especially microscopic sickling, is difficult to evaluate. However, even when content has been determined, there are not enough trained genetic counselors available. While there are persons trained in the medical-genetic aspect of this problem, training in the cultural, ethical, and sociologic factors which facilitate effective counseling is not generally available. Such training must also focus on the development of personal sensitivity and the communication process itself. Development of training programs in this field is urgently needed.

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The Medical "Generation Gap"

The report of the Second Triennial Survey of Attitudes of Medical Students and Recent Graduates appears elsewhere in this issue and continues a study initiated by the Committee on the Role of Medicine in Society several years ago. This unique study began its measurements of student attitudes at a time when the "generation gap" seemed like an abyss or chasm, difficult or perhaps even impossible to bridge across. The present report does much to restore confidence. It reflects not only a healthy respect for traditional values among students and recent graduates, but also a healthy determination to bring about change and with it progress.

More specifically, as the report states, it appears that medical education continues to convey many traditional professional values to students and it seems likely that tomorrow's students and practitioners will retain a core of these values. This is certainly reassuring. It is also a healthy sign that today's medical students perceive themselves as part of a larger structure for providing health care, an inevitable outgrowth of increasing specialization and increasing interdependence among specialists in medical practice and medical care. This too is reassuring. However, their more ready acceptance of a stronger governmental role and their apparently diminishing confidence in peer review and the profession's ability to discipline errant members are cause for pause. The definite trend away from early specialization seems in accord with the needs of the times; and the determination, even demand, to participate fully in decision-making augurs well for the future of the medical profession which now has great need to accomplish this at all levels of health care.

The Bureau of Research and Planning is to be congratulated for its continuing interest in this study and we already look forward to the next triennial report.

—MSMW

LETTERS *to the Editor*

Fatigue Caused by Vitamin E?

To the Editor: Because of the apparent "epidemic" which we all are seeing, of coronary heart disease, and also because of the simultaneous interest of the American public in vitamin E, early in 1972, I decided to review the available medical literature on the subject. I also included some personal correspondence with some of the most famous proponents of vitamin E therapy for a multitude of medical conditions. The conclusions of my reviews and correspondence were ambiguous. Because the only conclusion that I could draw from my studies was that vitamin E was harmless, even though its benefits were questionable, I decided to place a number of my patients on vitamin E. These patients included some with arteriosclerotic heart disease, but mostly men in their mid-thirties and early forties who were in excellent health at present as they had been in the past. I included myself and my partner in the study. Vitamin E in the form of D Alpha tocopherol was the formulation used, and the starting dose was 800 IU daily. The study was only an informal one and not controlled.

After about one week on the medication I began to feel an amazing weakness and fatigue as if suffering from a severe influenzal syndrome. The symptoms stopped after withdrawal of the vitamin E. Still thinking that I had likely suffered a viral illness, I resumed the vitamin E, and the symptoms returned. I did not relate this to my partner who also was taking the vitamin in the same dosage. When he left the office early two days in a row because he felt very tired and "sick," I related to him my experiences. He stopped the vitamin E and his symptoms disappeared the following day. By this time, virtually all of the patients and colleagues to whom I was giving the therapy were calling me and relating the same thing, and had to stop their vitamin E. Some, I among them, were able to tolerate the vitamin at 400 IU daily, with only minimal fatigue.

Now, in the course of my day-to-day practice of general and internal medicine, I see many people who have become obsessed with the megavitamin concept for "good health," and these people take literally handfulls of vitamins daily—usually the B complex, vitamin C and vitamin E. Many of these people have been coming into my office complaining of very severe fatigue. Very comprehensive workups are done along the traditional lines: physical examination, blood workup, urinalysis, stool examination, chest x-ray films, etc. These tests are inevitably negative and the overpowering fatigue responds promptly to the withdrawal of vitamin E.

I wish to report this observation, though it is uncontrolled, inasmuch as I cannot find it anywhere in the literature, and because my partner and I see it over and over, and we expect that in the vitamin conscious age in which we live, we shall see it more and more. We include it in our differential diagnosis of fatigue. In our busy practice we find "hypervitaminosis" E as a cause of fatigue to be less frequent than depression or menopausal syndrome but more frequent than anemia or hypothyroidism. In young patients, from whom a careful history is taken, it ranks second only to depression in our practice. Response to withdrawal of vitamin E is dramatic.

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Sylmar

Refer to: Valle RK: Prevention of smallpox in Alta California during the Franciscan Mission Period (1769-1833) (Medicine in Perspective). Calif Med 119:73-77, July 1973

Prevention of Smallpox in Alta California During the Franciscan Mission Period (1769-1833)

ROSEMARY KEUPPER VALLE, PhD, *San Francisco*

SMALLPOX WAS INTRODUCED into New Spain shortly after the conquest. In 1522, one of the men who accompanied Panfilo Narvaez from Cuba, where an epidemic was raging, brought the disease to Mexico with disastrous results. Graphic descriptions of this epidemic are found in Father Toribio de Motolinia's *Historia de los Indios de Nueva España*[1] and Father Bernardino de Sahagun's *Historia General de las Cosas de Nueva España.*[2] From that time forward smallpox epidemics broke out periodically with varying degree of severity, and this disease was a major factor in the decimation of the Indian population of Baja California.[3]

But while authors such as James O. Pattie,[4] Sherbourne F. Cook,[5] Henry Harris[6] and others refer to the devastating effects of smallpox on the Alta California Indians, investigation of the original mission records reveals no evidence that any epidemic of the disease occurred during the Franciscan Mission Period. Doubtless the relative isolation of the area contributed to this escape, at least during the first few decades of the period, but a factor of much greater importance was the preventive measures taken by the Spanish and Mexican governments and the missionaries. These measures were the early use of quarantine, isolation and immunization by variolation and vaccination to prevent the introduction and spread of the disease.

What was probably the first smallpox scare was dealt with by quarantine and isolation. It occurred in August of 1781 when a group of soldiers and colonists arrived near Mission San Gabriel Arcángel from Baja California where an epidemic was in progress.[8] Governor Felipe de Neve, in a letter to the Comandante General de las Provincias Internas dated October 29, 1781, states that the new arrivals had been placed under quarantine at some distance from the mission because several of the children were convalescing from smallpox.[9]

A further effort to control smallpox was a Royal Cedula, issued by King Charles III of Spain, which ordered that the book *Disertacion Fisico-Medica en la cual se Prescribe un Metodo Seguro para Preservar a los Pueblos de Viruelas hasta Lograr la Completa Extincion de Ellas en Todo el Reyno*[10] be distributed throughout the Spanish possessions in the New World. This book was written by Don

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At the time this paper was submitted for publication, January 19, 1973, the author was a candidate for PhD in the History of the Health Sciences Department, University of California, San Francisco, School of Medicine.

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Francisco Gil, Surgeon of the Royal Monastery of San Lorenzo and member of the Royal Academy of Medicine of Madrid. Don Josef de Galvez, Marques of Sonora, transmitted this order to New Spain along with 150 copies of the book.[11] On September 15, 1786 Brigadier Jacobo Ugarte y Loyola, military governor of New Spain, sent a letter to Governor Pedro Fages of California stating that he was forwarding a copy of the Royal Cedula and 20 copies of the book.[12] These were to be distributed in both Baja and Alta California and while it is not known how many copies were actually received at the missions, there is a well-thumbed copy of the book in the Santa Barbara Mission Archives. Gil's book does not denigrate the effectiveness of inoculation, but emphasizes the importance of quarantine and isolation in the control of smallpox, giving much attention to the supportive measures to be used in the treatment of those who are stricken with the disease. It is mentioned in the foreword of the book that the methods described by the author had been used with good result in combatting a smallpox epidemic at New Orleans on the Mississippi River.

On February 28, 1797, as a result of the outbreak of smallpox in Mexico and Guatemala, Don Miguel de la Grúa y Branchiforte, Viceroy of New Spain, issued an edict containing thirteen sections of instructions on how to prevent and deal with a smallpox epidemic.[13] For the most part it is a summary of the methods proposed by Dr. Gil in his "Disertacion" which the Viceroy had ordered reprinted in Mexico in 1796. Section eight of this instruction specifically mentions inoculation.

> When the latter (smallpox) becomes widespread, because of the inability to stop it at the beginning by the appropriate methods indicated, it will be advisable to put inoculation into practice, pointing out to those concerned, in order that they may adopt it voluntarily, its advantages and the great success obtained in Oajaca, Tehauntepec and other cities, where the results have been exceedingly favorable to mankind.

Governor Diego de Borica acknowledged receipt of these instructions on July 20, 1797, and stated that he was transmitting them to his company commanders.[14] On April 15, 1798, Lt. Jose Arguello, commander of the Presidio of San Francisco, wrote to Governor Borica that he had received and duly noted the Viceroy's edict regarding smallpox.[15]

The second smallpox threat to Alta California occurred early in May of 1798 when the "Concepcion," the regular ship from San Blas, arrived in Santa Barbara harbor with several persons who had smallpox. The passengers were quarantined on the ship from May 3 to May 16, and while this period evidently was sufficient to prevent the introduction of the disease, Governor Borica thought it should have been prolonged.[16] In accordance with Viceroy Branchiforte's instructions, he notified the Presidio commanders and Father Fermin Francisco Lasuen,[17] the president of the missions, of the incident and advised inoculation.[18]

A direct result of this episode was the circulation through Alta California of an instruction on how to perform inoculations. It was written by Dr. Pablo Soler, the military surgeon at Monterey and the only physician in the province at the time, and endorsed by Governor Borica. Copies of this instruction are found in the Santa Barbara Mission Archives and the archives of Mission Santa Clara de Asís. Because of its rarity and explicitness about the method to be employed, the complete document is presented in translation.

> Method of performing inoculations against smallpox by which simple operation experience in New Spain has shown numerous fatalities are avoided.
>
> Wet the point of a lancet or similar instrument with smallpox pus; introduce the lancet thus anointed beneath the skin in the web between the index finger and the thumb, so superficially that hardly any blood appears; then place the finger on top of the wound when removing the lancet so that the pus will remain. Do not appy a bandage until the blood has dried.
>
> The food should be light and strengthening, such as *atole* of barley, corn, etc.; drink the same, such as water of lettuce or maiden hair; and rest. Do not give medicine or other restoratives.
>
> All ages can be inoculated even if they suffer from the itch or some similar disease. Above all, cleanliness, fresh air and well-being are recommended in addition to all that indicated in smallpox which occurs naturally.
>
> I do not doubt that the reverend missionaries will secure this blessing for the neophytes in view of the havoc wrought among the Christian Indians as well as the non-Christian savages in Baja California in 1781. Fortunately, San Fernando and San Borja escaped the contagion because of the inoculations which were carried out by Father Crisostomo Gomez with the usual happy results.
>
> We would wish that this blessing will reach the poor non-Christian Indians through their

relatives, for these writings are directed to the good of Humanity.

> *Monterey, 17th May 1798* *(Signed)* PABLO SOLER
> *For the Reverend Missionaries of San Carlos*
> *(Signed)* BORICA

There can be no doubt that this instruction was prepared for use by the missionaries or that they actually performed inoculations.

On May 25, 1798, Captain Jose Arguello of the Presidio of San Francisco, wrote to Governor Borica that he had received his letter and the *Metodo para Practicar la Ynoculacion* and that he was sending copies to his troop commanders and Missions San Francisco de Asís, San Jose and Santa Clara de Asís, so that it could be put into practice. He further stated that if the disease broke out, he would have his family inoculated as an example to others.[19]

Finally, on September 4, 1798, Governor Borica wrote to Viceroy Jose Miguel de Azanza that smallpox had not been introduced into the province of Alta California at this time.[20]

Early in 1804, there was a flurry of interest in New Spain in vaccination against smallpox when Dr. Alejandro Arboleya of the Royal Spanish Navy arrived with some vials of vaccine matter and successfully vaccinated a number of orphans in Mexico City. In April, 1804, the *Gazeta de Mexico* which was widely distributed in both Baja and Alta California published a two-part supplement about the procedure.[21] It states that if directions are followed carefully, anyone can vaccinate. The vaccine matter should be introduced beneath the skin by a lancet, knife or needle and the preferred site is the anterior surface of the upper arms. As can be seen in Figure 1, the illustration which accompanied the article, multiple vaccinations were performed on each subject.

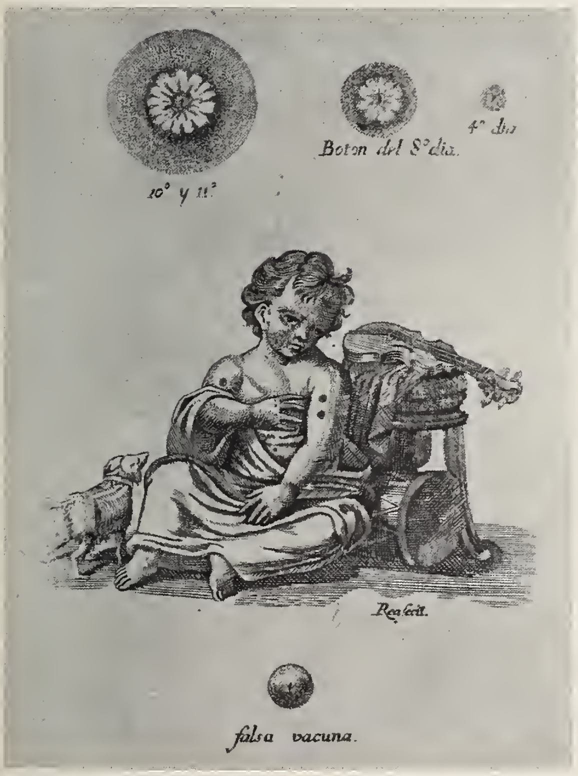
Boton del 8° dia.
4° dia
10° y 11°
Rea fecit.
falsa vacuna.

Figure 1.—At top is the type of lancet in use at the time. Also shown is the appearance of the pustules at 4, 8, and 10 and 11 days after vaccination. Subject has received multiple vaccinations. At the bottom is appearance of false vaccination.

Gazeta de Mexico, April 1804—*Courtesy of Bancroft Library*

Despite this earlier vaccination campaign, probably the most famous of all efforts to eliminate the scourge of smallpox in the Spanish possessions was the expedition of Dr. Francisco Xavier de Balmis. This vaccine expedition was undertaken at the instigation of Dr. Josef Ignacio Flores who had been born in the New World but who was serving as one of the court physicians in Spain in 1803.[22] The purpose of the expedition was to introduce vaccination into the Spanish overseas possessions, and it departed Spain on November 30, 1803, and arrived at Vera Cruz, Mexico on October 27, 1804, after stops at ports in the Canary Islands and northern South America.

On November 27, 1804, the Bishop of Sonora, Francisco Rouset de Jesus, who had jurisdiction over the California missions, wrote to Father Estevan Tapis, the president of the missions, announcing the visit of Dr. Balmis and instructing the missionaries as follows:

> Since it is in accord with our obligations to cooperate efficiently, to put into practice and to make effective the sovereign will of the King by aiding and assisting as much as possible, the individuals and doctors who compose the charitable expedition already mentioned, I charge you that you shall send this communication to all the missions in your jurisdiction for execution of its requirements and that you retain the original in your archives and that you notify our private secretary of your compliance.[23]

For some unexplained reason, no member of the Balmis expedition visited California, but this letter no doubt served to focus attention on the problem of smallpox and its control.

The next mention of smallpox comes from Dr. Georg H. Langsdorff, the German-trained physician who accompanied Russia's Resanov Expedition to California in 1806. He mentions in his report of this visit that Governor Jose Joaquin Arrillaga had told him that vaccination had been used in California for many years. He further states that he was told that cowpox had been present in the cattle in the area south of Monterey for a long time and that it had been used for the successful immunization of many people. In fact, the inhabitants had so forgotten the dangers of smallpox that, as a consequence, they had become negligent about being immunized.[24] This statement suggests the possibility that vaccinations were performed in California as early as in the eastern United States, if not earlier.

In January, 1810, the Spanish government authorized Dr. Francisco X. de Balmis to return to New Spain on a second vaccination expedition.[25] After his arrival in Mexico, he issued a broadside, *Reglamento de Orden de S. M. para que se Propague y Perpetue La Vacuna en Nueva España,* a copy of which is found in the archives of Mission Santa Clara de Asís. This is dated October 10, 1810, and concerns the methods to be used for the preservation of the vaccine and for setting up vaccination stations. He remarks herein that although vaccine matter preserved in sealed vials of glass or wax, scabs, or pus dried on threads, splinters or quills had all been used for vaccination, the best results were obtained by arm to arm transfer of the pus.[26] Balmis, in his *Tratado Historico y Practico de la Vacuna* which was widely distributed in Spain and her possessions, makes the usual statement that vaccination can be performed by anyone. He also points out that while four vaccinations on a subject are sufficient, 10, 12 and even more have been performed without untoward effect.[27]

Activity regarding vaccination seems then to have subsided for a time—or at least it is not mentioned in the available records until 1817. At this time, according to Hubert H. Bancroft, Jose Verdia[28] brought some vaccine matter to Monterey. No additional information on this point could be found, however.

In 1821, the Russian ship "Kutusoff" landed at Monterey with vaccine lymph which had been obtained in Lima, Peru. Approximately 90 children were vaccinated with this material, but on September 13, 1821, Governor Pablo Vicente Sola writes that the procedure had been a failure because the vaccine matter had lost its effectiveness.[29]

Evidently procurement of effective vaccine matter was a great problem in Mexico and California. On August 27, 1823, Lucas Ignacio Alaman, the Mexican Secretary of State, wrote to the governor of California as follows:

> The supreme executive power has directed his attention to the conservation and propagation of the vaccine fluid, noting with considerable anxiety that a preventative so efficacious against epidemics of smallpox has almost disappeared from our midst. The Municipal Councils, Provincial Deputations and local functionaries are responsible for the public health. These authorities are charged with the encouragement of the propagation of so precious a fluid. Therefore, in order that the inhabitants may guard against this plague, His Highness desires that you proceed at once, in conjunction with the Provincial Deputation and the Board of Health, to obtain vaccine from the nearest source. We have been advised that it may be preserved by transporting it in thin gut or glass containers. If such means do not suffice, then vaccinated children should be sent from one place to another at the expense of the respective municipalities . . . [30]

There is no evidence that these recommendations were ever carried out in California, perhaps because a vaccine source existed in cattle in the Monterey area. However, it is interesting to note that arm to arm transfer from child to child was still considered the best method for preserving and transporting the vaccine matter.

The next statement regarding smallpox in Alta California is that of James Ohio Pattie, a fur trader and prospector who arrived on the Pacific coast in 1828. He states in his "Personal Narrative" that an epidemic of smallpox broke out in 1828 and caused many deaths.[4] Investigation of the original mission records and an epidemiological study of the 1827-28 epidemic reveal that it was due to measles and not to smallpox, and that none of Pattie's statements correspond to the extensive contemporary evidence.[31] Pattie also mentions that he vaccinated 22,000 persons against the disease[32] but scrutiny of this assertion and comparison with the records shows that he claims to have vaccinated 6,000 more persons than were actually present in the 14 missions he is supposed to have visited.[31] In fact, search of the original mission records fails to reveal any evidence of Pattie's tour,[31] a fact also noted by Bancroft in his *History of California.*[33]

Bancroft mentions that the Russians again brought smallpox vaccine to San Diego and Monterey in 1829.[34] At this time William A. Richardson was hired to vaccinate in the missions and thus earned his nickname "Doc."[35]

Governor Manuel Victoria mentions in a report to Mexico dated June 7, 1831, that vaccinations were being and had long been carried out by amateurs because there were no professionals to perform them and that smallpox was unknown in Alta California.[36]

The reports of two foreign visitors are worthy of note because they attest the absence of smallpox in Alta California. Captain Frederick W. Beechey who sailed up and down the California coast in the English ship "Blossom" during the years 1826 through 1828 mentions in his *Account of a Visit to California* that it was obvious there had been no smallpox in Alta California for many years.[37] Auguste Bernard du Haut-Cilly, Captain of the French ship "Le Héros," who visited many of the missions, states in his *Voyage autour du Monde, 1826-1829* that it was apparent that the Alta California natives had escaped the ravages of smallpox.[38]

Further, Father Zephryin Engelhardt who devoted a lifetime to the study of the missions, states in his *Missions and Missionaries* that the precautions taken by the government and the missionaries seemed to have prevented the spread of epidemics other than measles and fevers, and that there is no record of smallpox having occurred before 1838.[39]

From a perusal of the foregoing it becomes apparent that there were no smallpox epidemics in Alta California during the Franciscan Mission Period (1769-1833) and there can be no doubt about the concern of the government and the clergy for the prevention of this disease. Their achievement in this respect was remarkable, especially in view of the terrible havoc caused by smallpox in many other parts of the world.

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Another Look at the Medical "Generation Gap"

Second Triennial Survey of Attitudes of Medical Students and Recent Graduates

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A Socioeconomic Report of the Bureau of Research and Planning, California Medical Association

A 1969 survey of attitudes held by medical students and recent graduates was repeated in 1972, using the same samples of respondents and adding a new freshman group. Findings from both surveys showed that a "generation gap" existed on many issues.

Furthermore, a comparison of the two studies suggested that two kinds of attitude change are occurring simultaneously. On some issues, the next generation of physicians will probably continue to differ from their predecessors. Perhaps the primary thread woven through this cluster of attitudes is that today's medical students and young physicians perceive themselves as members of a larger structure for providing health care.

However, many of the students' attitudes held early in their medical careers appear to have been modified in the process of becoming physicians. It appears that medical education continues to convey many traditional professional values to students, and it seems likely that tomorrow's physicians will retain a core of those values.

THE DECISION TO CONDUCT the first Survey of Attitudes of Medical Students and Recent Graduates grew out of concern about an apparent "attitude gap" between medical students and older physicians. In 1967, the California Medical Association's Committee on the Role of Medicine in Society requested the Bureau of Research and Planning to study this problem, for which there were no available data.

An extensive questionnaire was sent to a random sample of one-third of all first and fourth year students in California medical schools and to one-third of those who graduated in 1965. Response rates were excellent, exceeding 65 percent in all groups.

The results of that study showed agreement on some issues and disagreement on many others, thus confirming that a "generation gap" did exist. It was still unknown, however, whether these disparities in attitude were a temporary reflection of differences in age and experience, or were a sign of changing goals and attitudes that would characterize a new generation of physicians.

The first report, "Survey on Medical Student Attitudes," was printed in CALIFORNIA MEDICINE, Volume 111, December, 1969, pages 501-504.

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Reprint requests to: Bureau of Research and Planning, CMA, 693 Sutter Street, San Francisco, CA 94102.

Therefore, an essentially similar survey was conducted in May 1972 with a new freshman group, but otherwise using the same samples. Some questions that no longer seemed relevant were deleted from the questionnaire, and some new items of current interest were added.

With the results of this study, it was possible to observe changes within age groups over the three-year interval, as well as differences between groups. For example, it was possible to study how the attitudes of the class of 1972 changed in the transition from freshmen to seniors, as well as to compare the thinking of today's freshmen with that of freshmen three years ago.

Findings

The information gained in this study suggests that two kinds of changes in attitude are occurring simultaneously. As students advance in their careers, they tend to share more opinions with their older colleagues. But at the same time, the values of society as a whole appear to be changing, with the effects of this change felt most deeply by the young. In this case, the students' attitudes predict the values of the next generation of physicians. The results of the study suggest that physicians in the final quarter of the 1900's will have a different conception of their role and their relation to society, to government, and to other professions. A common idea seems to link these new attitudes together: that physicians in the future are likely to perceive themselves less as individualists within a brotherhood of peers and more as members of a larger structure for providing health care.

Medical Care as a Right

More than two-thirds of respondents in all groups in both survey periods agreed with the statement "Medical care for every individual is a right, not a privilege."

Chart 1 shows very little difference between groups at the same point in their medical career. For example, 72.3 percent of seniors agreed with the statement in 1969 and 73.3 percent agreed in 1972.

Within groups of the same respondents, the classes of 1969 and 1972 have each decreased slightly in their level of agreement. This pattern conforms with the expectation that as respondents grow older, their thinking becomes more "conservative" or traditional.

However, this expectation is sharply contradicted by the behavior of the class of 1965. In 1969, only 69.5 percent of these respondents agreed with the statement; in 1972, 80.8 percent agreed. This shift—which is larger than that of any other group—suggests that these practicing physicians may have been influenced by a widespread change in American cultural values. However, the change may be less a philosophical shift than an acceptance of the inevitable—the fact that most Americans have come to believe that medical care is indeed their right.

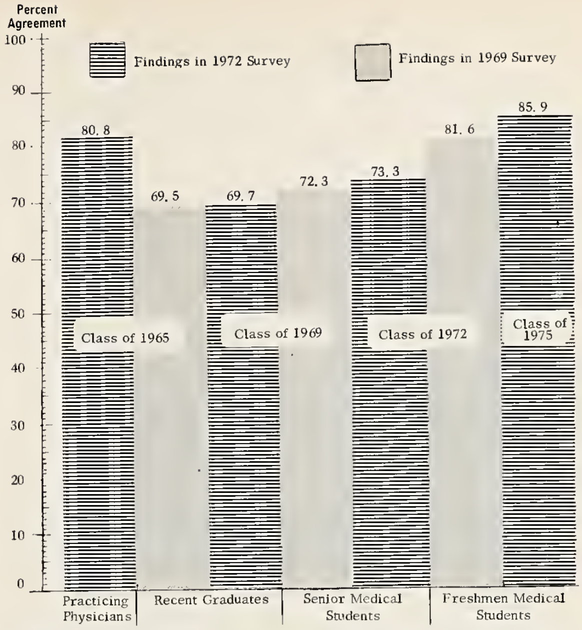

Chart 1.—Percent of respondents in 1969 and 1972, by class, who agreed with the statement: "Medical care for every individual is a right, not a privilege."

More Support for Government's Role

Responses to statements dealing with the role of government and other agencies in health care indicate that medical students and young physicians generally have come to accept this fact of life more willingly during the past three years.

More than two-thirds of both freshmen and senior medical students currently feel that government has a role in establishing quality standards. This proportion represents a significant increase during the three-year period. However, only about half of the recent graduates and practicing physicians agree with the concept. Their attitudes have remained virtually constant since 1969. Hence it is plausible to conclude that attitudes on this issue tend to solidify after medical school graduation and appear resistant to outside forces.

To illustrate the trend in attitudes about the role

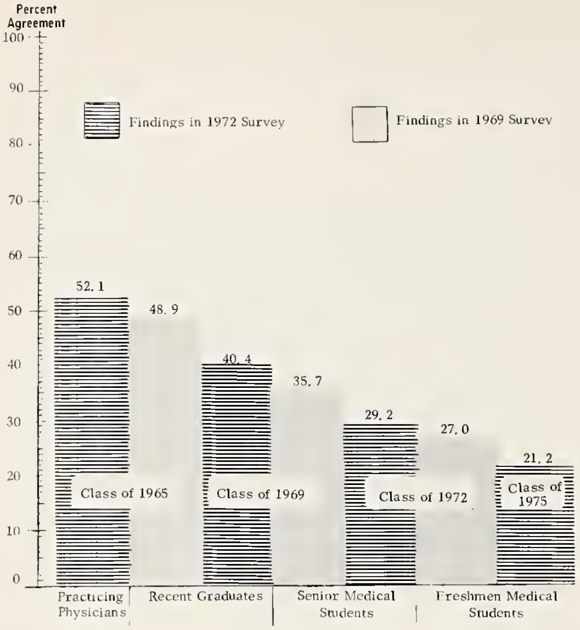

Chart 2.—Percent of respondents in 1969 and 1972, by class, who agreed with the statement: "The government should have no voice in determining how physicians practice medicine."

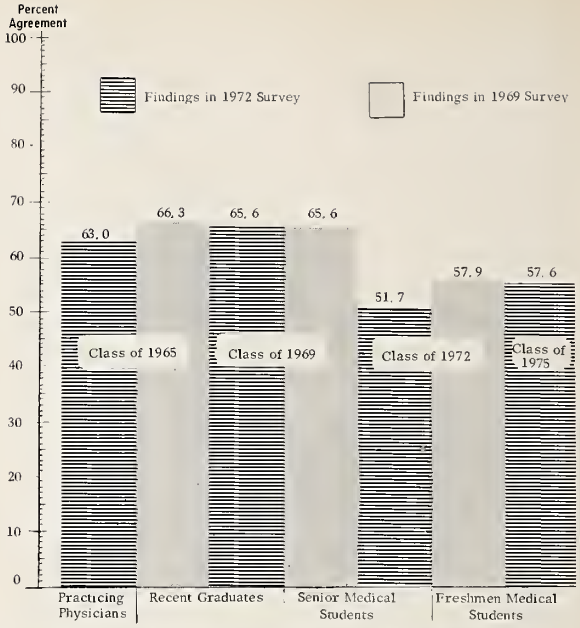

Chart 3.—Percent of respondents in 1969 and 1972, by class, who agreed with the statement: "If local medical societies were to offer affiliate membership to medical students at nominal costs, and encourage students to engage in society activities, both organized medicine and the student would benefit greatly."

of government and other agencies in medical practice, Chart 2 provides information about levels of agreement with the following statement: "The government should have no voice in determining how physicians practice medicine." As can be seen in the chart, agreement with this concept has declined during the three-year period among respondents at all levels—freshmen, seniors and recent graduates. Among this last group, in fact, there was a significant decline from 48.9 to 40.4 percent agreement with the statement.

Nevertheless, the chart clearly indicates that as medical students and recent graduates progress in their careers, their feeling grows that government's role should be limited. Note, for example, that 40.4 percent of the class of 1969 now agree with the statement while three years ago, when they were in medical school, just 35.7 percent agreed. This progression of opinion is obviously tempered by the general shift in attitudes discussed above.

Participation in Organized Medicine

Student responses concerning their involvement in organized medicine show some increasing skepticism or disinterest toward mere involvement, but a high degree of interest if such involvement implies participation in the decision-making process. The majority of respondents in all groups, particularly interns and residents showed enthusiasm for involvement in the California Medical Association and local societies.

Young physicians showed considerable optimism that they can influence the policies and direction of the American Medical Association if they become involved, with more than three out of five recent graduates and practicing physicians agreeing with a statement to this effect. Even among freshmen students, the majority who gave an opinion agreed that young physicians can be influential. It is important to note that among respondents in the class of 1965, more than three agreed with the statement for everyone who disagreed.

Chart 3 provides information about levels of agreement with the following statement: "If local medical societies were to offer affiliate membership to medical students at nominal cost, and encourage students to engage in society activities, both organized medicine and the student would benefit greatly." This statement was used in the 1969 and 1972 surveys, and in both years over half of all groups supported it. During the three-year interval between surveys, there was almost no change among recent graduates and freshmen. However, the rate of agreement among senior medical students declined sharply, from 65.6 to

51.7 percent. Local medical societies may consider this a disappointing response, since it suggests that the past three years of student involvement—or non-involvement—have not been entirely successful.

More Resistance to Specialization

Some of the most striking changes among respondents over the three-year period between surveys concerned their concept of the physician's role and how he can best be educated to fulfill it. In particular, a clear trend away from a belief in the advantage of early specialization is evident among all age groups in the survey.

All groups also showed growing resistance to further specialization and consequent limitation in community and environmental health fields during the period of medical training. In 1969 recent graduates were most likely to have agreed with the appropriateness of a trend toward further specialization. It is this year's recent graduates whose opinions changed most sharply over the three-year period.

As might be expected from the above responses, all groups of respondents strongly supported greater emphasis on community and environmental health in medical education.

Chart 4 contains information about the pattern of agreement with the following statement: "Continuing advances in science and technology point to the probability that the physician of the future will become more of a technician and less of a personal physician." Today's younger respondents clearly feel that technology does not pose a great threat to their role as personal physicians, whereas in 1969 the younger respondents showed a relatively high level of agreement. In 1972, respondents at all levels were less likely to agree with the statement; furthermore, the younger the group, the larger the shift. The rate of agreement among freshmen dropped from 49.7 to 29.3 percent. Seniors and residents were also less likely to agree, although the decline was not as dramatic as among freshmen.

An "attitude gap" between age groups has developed in the past three years. The oldest group (the class of 1965) has retained virtually the same opinions, while the youngest class (the class of 1972) recorded a drop from 49.7 to 35.8 percent. Since younger respondents may have acquired a familiarity with technology at an earlier age, perhaps their response shows that they feel more confident in their ability to direct the application of technology toward their own goals.

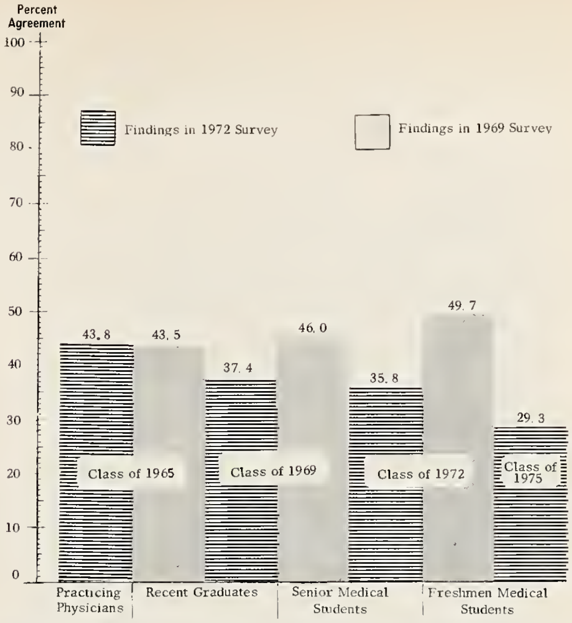

Chart 4.—Percent of respondents in 1969 and 1972, by class, who agreed with the statement: "Continuing advances in science and technology point to the probability that the physician of the future will become more of a technician and less of a personal physician."

The total pattern points to optimism among medical students that the personal physician is not destined to become an extinct species. Disquieting, however, may be the opinion held by almost half of today's younger practitioners, represented by the class of 1965, that tomorrow's physician may no longer be cast in that personal role.

Correcting Manpower "Shortage"

Respondents at all levels showed a high degree of agreement with a statement that the "physician's assistant" can meet a real need in health care delivery.

Differences of opinion were evident, however, about the need for more physicians. As seen in Chart 5, more than three-quarters of practicing physicians agreed with a statement that apparent shortages of physicians are the result of maldistribution rather than inadequate numbers. However, agreement with the statement declines in the younger groups: 69.7 percent of recent graduates, 63.3 percent of seniors, and just 46.0 percent of freshmen agreed. Among freshmen, more than 40 percent disagreed with the statement, implying that they believe that there are not enough physicians being graduated from medical school to meet the country's health need. Interestingly, this age

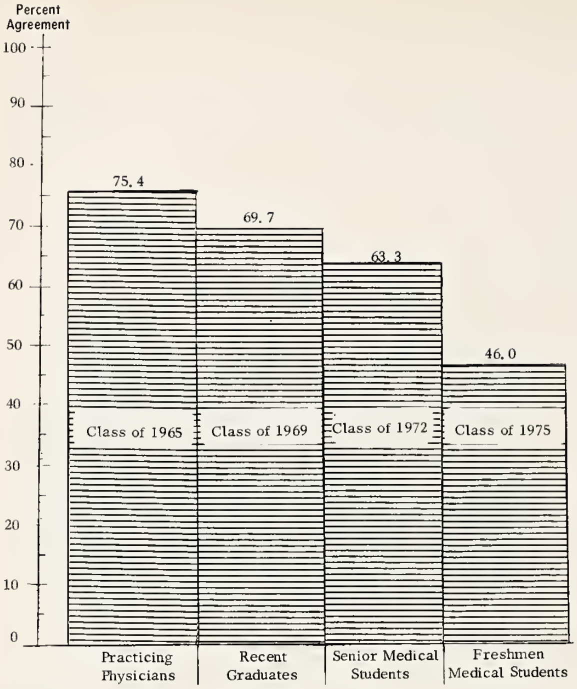

Chart 5.—Percent of respondents in 1972, by class, who agreed with the statement: "Apparent shortages of physicians are really based on maldistribution, inefficient utilization rather than inadequate educational output."

correlation appears to continue, with older physicians less convinced that an absolute shortage exists. California data extracted from a recent AMA survey,* for example, showed that just 12.2 percent of AMA members feel that there is a serious shortage of physicians in their immediate areas.

National Health Insurance Needed

A large majority of all groups believes that some kind of national health insurance is needed.

Among the three older groups, there was an even higher level of support for a nationalized plan of catastrophic coverage. More than three-quarters of the practicing physicians, 87.9 percent of recent graduates and 82.5 percent of seniors found this type of plan desirable.

Over 75 percent of both student groups supported restructuring of the system of health delivery if a national health insurance is adopted. Understandably, however, the reaction from the two older groups was more mixed, with 59.6 percent of recent graduates and 50.6 percent of practicing physicians agreeing with the statement. Nevertheless, it is significant that even among the medical school class of 1965, more than half of all respondents favored restructuring. Since the question was not asked in 1969, there are no data to suggest a trend in attitudes.

Hospitals Seen as Health Centers

Although a high level of support for a general restructuring of the system was expressed by students, both seniors and freshmen had mixed reactions to expansion of the role of the medical school. In response to a statement that medical schools should assume a central role in determining the nature and quality of community health services, only about half of both student groups agreed. Recent graduates showed a slightly higher level of support, with 57.6 percent agreeing, while only 41.1 percent of practicing physicians agreed with the statement.

Furthermore, the trend over the past three years is toward less support for an expanded role of medical schools. Among groups at the same level in their medical careers, only recent graduates had a higher rate of agreement in the 1969 survey. Agreement declined among all groups of the same respondents during the three-year interval between surveys. The greatest drop, about 12 percent, came between freshmen and senior years in medical school.

Responses illustrated in Chart 6 indicate a high level of support for an expanded hospital role in community health care. In 1972, the strongest support came from freshmen medical students and from recent graduates. This year's seniors, however, showed a relatively low level of agreement. Although practicing physicians were least likely to support the concept, the proportion who agreed was still a substantial 63 percent.

However, decreases in support for the statement since 1969 are clearly shown in the chart. The trend that emerges is similar to the trend in attitudes toward the role of medical schools, with a general decline in agreement among comparable levels as well as among groups of the same respondents over the past three years. To a certain extent, these trends may reflect the resurgence of interest in the personal role of the physician discussed earlier.

Stricter Professional Standards

Among the three younger groups in the survey, there was extremely strong support for periodic licensing of physicians and little confidence in the medical profession's current efforts in peer review and in disciplining errant physicians. The trend in the past three years, furthermore, is toward even less confidence.

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*American Medical Association, Center for Health Services Research and Development: 1972 Opinion Survey of the AMA Membership

Agreement that relicensing should be supported was quite high in 1969, generally lower in 1972. The proportion of freshmen increased from 66.5 percent to 78.2 percent, but the proportion of seniors agreeing declined from 80.3 to 74.2 percent. This compares closely with a figure of 68.0 percent recorded nationally in a recent study conducted among senior medical students by Medical Economics magazine.* Most striking was the substantial difference in attitude of recent graduates; 78.8 percent now support relicensing, compared with 54.3 percent three years ago. Furthermore, the level of support for the concept among the class of 1965 increased substantially to 63 percent during the three-year period.

A similar pattern emerged in response to a statement that the profession is meeting its obligations in disciplining physicians. While freshmen tend to be unacquainted with the subject, more than half of all other respondents think the profession should be doing more. The three-year trend revealed declines in the proportion of respondents at the same level, as well as among the same respondents, who feel that the profession is meeting its disciplinary obligation.

Expanded Peer Review

A statement that the medical profession is meeting its obligation in peer review drew divergent responses from different age groups in the survey. These complex data are illustrated in Table 1, which shows the percentage of those who disagreed and who were either indifferent or did not answer, as well as the percentage agreeing.

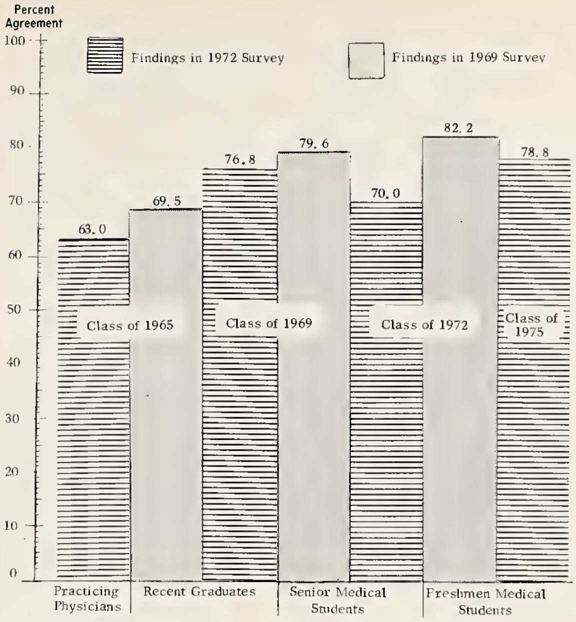

Chart 6.—Percent of respondents in 1969 and 1972, by class, who agreed with the statement: "Hospitals should serve as community health centers responsible for making available comprehensive health care to the public."

The only pattern that applies to all groups is a sharp decline in the rate of responses of "indifferent" or "no answer."

These findings demonstrate a significantly increased awareness of what the medical profession is doing in peer review. As a result of new awareness, members of responding groups have taken stronger positions. In the two student groups, this polarization has led to a simultaneous increase in both approval and disapproval of current peer review efforts, with the trend toward disapproval predominating. For example, seniors increased in their rate of agreement with the statement by 2.7 percent; simultaneously, however, the rate of disagreement increased by 15.9 percent.

Among groups of the same respondents, all groups showed simultaneous increases in both

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*What the next medical generation wants. Medical Economics 49:191-206, September 11, 1972

TABLE 1.—*Percent of Respondents in 1969 and 1972, by Class, Who Indicated That the Medical Profession Is Successfully Meeting Its Professional Obligations in the Area of Peer Review.*

	Class of 1965		*Class of 1969*		*Class of 1972*		*Class of 1975*
Opinion	*1972 7-year graduates*	*1969 4-year graduates*	*1972 3-year graduates*	*1969 (as seniors)*	*1972 seniors*	*1969 (as freshmen)*	*1972 freshmen*
Agree	45.2%	31.5%	17.2%	24.6%	27.5%	16.3%	21.2%
Disagree	50.6	43.5	72.8	47.4	63.3	24.8	40.4
Indifferent or No Answer	4.1	25.0	10.1	27.7	9.1	58.9	38.4
Total Percent*	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Total Respondents	73	92	99	137	120	185	198

*Totals may not add to 100.0% because of rounding.

agreement and disagreement, except for the class of 1969, where rate of agreement decreased by 7.6 percent. Only among the class of 1965, the oldest group included in the survey, did the increase in agreement exceed the increase in disagreement.

Despite the complexity of the response pattern, trends are clearly evident toward increased awareness of peer review activities and toward decreasing confidence that the medical profession is fulfilling its responsibilities in this area.

A statement that the profession is meeting its responsibilities in continuing education drew more support than did the previous two questions. The proportion who agree reached 78 percent among physicians, with recent graduates and seniors only slightly below this figure. All groups at comparable professional levels have increased their rate of agreement since 1969.

Larger Social, Environmental Roles

Responses to questions about the profession's social and environmental responsibility revealed a consensus among the three younger groups that the profession is not meeting its obligations in these areas.

Furthermore, less than 15 percent of each of the three younger groups feel that the medical profession is sufficiently involved in comprehensive health planning. Among the oldest group, the young practicing physicians, this proportion is less than a third.

The data also illustrate a growing awareness of comprehensive health planning during the past three years. Among all groups there was a decline in the proportion who indicated indifference or did not respond to the specific statement.

Personal Career Choices

In addition to questions about attitudes on current issues, the questionnaire also contained a preliminary section on career preferences. Both the 1969 and 1972 forms asked for an indication of specialty interest; the 1972 form also asked respondents what type of practice they prefer, and whether they would be willing to practice in an urban ghetto or a rural setting.

Specialty Interest

The data about respondents' specialty interest outlined in Table 2 show a growth of student interest in family practice. The proportion of respondents choosing a type of primary care specialty—including general or family practice, internal medicine, pediatrics, or obstetrics-gynecology—increased dramatically in the past three years, particularly among the younger groups. In 1969, a little less than half of freshmen planned to practice as primary care physicians, compared with nearly three-quarters of freshmen in 1972.

The primary care area that drew the greatest increase in interest was general or family practice. In 1969, this field was the choice of less than 10 percent of freshmen; in 1972, more than a third chose general or family practice. Internal medicine drew a slight increase in interest, while obstetrics-gynecology and pediatrics both decreased slightly.

During the three years, the same respondents do not appear to have lost interest in primary care fields. Note that among each graduating class an even larger proportion have entered or currently intend to enter primary care specialties in 1972 than those who intended to three years ago. Among the class of 1969, many of whom have probably made a final choice of specialty in the

TABLE 2.—*Percent of Respondents in 1972, by Class, Who Indicated Their Specialty Interest*

	Class of 1965		*Class of 1969*		*Class of 1972*		*Class of 1975*
Specialty Interests	*1972 7-year graduates*	*1969 4-year graduates*	*1972 3-year graduates*	*1969 (as seniors)*	*1972 seniors*	*1969 (as freshmen)*	*1972 freshmen*
General or Family Practice	11.0%	4.8%	11.2%	4.6%	11.9%	9.8%	34.9%
Internal Medicine	12.3	16.9	11.2	18.3	30.0	17.0	20.0
Pediatrics	8.2	8.4	11.2	8.4	11.0	16.1	14.9
Obstetrics/Gynecology	2.7	0.0	18.4	9.9	7.6	3.6	2.3
All Primary Care	34.2	30.1	52.0	41.2	60.5	46.4	72.1
Other Specialties	65.7	69.9	48.5	58.8	42.5	53.6	36.4
Total Percent*	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Total Respondents	73	83	98	131	118	112	175

*Totals may not add to 100.0% because of rounding.

past three years, the proportion of those choosing a type of primary care rose from 41.2 to 52.0 percent.

Type of Practice

Table 3 illustrates some divergence between the type of practice in which students expect to engage and the type in which the class of 1965 is currently engaged. Among practicing physicians who responded, a large proportion—31.5 percent—are in private partnership while another 20.5 percent are in solo practice and 19.2 percent are in private groups. Data from the class of 1969 are not entirely valid, since many are still in residency and thus have indicated "hospital-based practice." Nevertheless, it is clear that the proportion of the class of 1969 who are either currently practicing in private groups, or who plan to do so, is increasing. Furthermore, about two out of five freshmen and senior medical students plan to practice in groups. Perhaps the distinction between partnerships and groups is not clear among respondents who have not yet entered private practice—many who have indicated a preference for "groups" may merely mean a multi-specialty environment comprised of a relatively large number of physicians. Since this question was not asked previously, it is not possible to determine trends in choice.

Interest in private solo practice does not appear to be great among any of the three younger groups. While over 20 percent of the class of 1965 ultimately chose this mode, only about 10 percent of physicians in training plan to do so. Particularly interesting is the fact that the most recent data available show that over half of all active nonfederal physicians in California were in individual practice in 1969.[*] On the other hand, interest in a hospital-based practice is relatively high among students, with 20 percent or more planning to practice in this framework. Regard for teaching and research is lower in the younger groups, suggesting that they are at present more clinically than academically oriented.

TABLE 3.—*Percent of Respondents in 1972, by Class, Who Indicated the Types of Practice They Are Focusing (Plan to Focus) on in Their Medical Career*

	Class of 1965 (7-year graduates)	*Class of 1969 (3-year graduates)*	*Class of 1972 (seniors)*	*Class of 1975 (freshmen)*
Private solo ...	20.5%	9.1%	8.3%	10.1%
Private partnership ..	31.5	18.2	20.0	15.7
Private group ..	19.2	36.4	39.2	41.9
Hospital based .	9.6	24.2	20.0	21.7
Teaching	6.8	5.1	3.3	1.0
Research	1.4	0.0	0.8	0.5
Other	8.2	4.0	5.8	4.0
No answer	2.7	3.0	2.5	5.1
Total percent*	100.0	100.0	100.0	100.0
Total respondents	73	99	120	198

*Totals may not add to 100.0% because of rounding.

Urban Ghettos and Rural Areas

Freshmen medical students indicated a high level of interest in practicing in urban ghettos or rural communities, as shown in Table 4. Almost a quarter of freshmen said that they are considering practicing in an urban ghetto and over half are considering practice in a rural setting. Whether students will later translate these preferences into action can merely be a source of speculation at this time.

Seniors are equally interested in rural areas, less interested in urban ghettos. The difference between freshmen and seniors in their interest in urban practice areas undoubtedly stems from recent changes in composition of medical students. As entering freshmen, the California class of 1972 was 94.8 percent white. Although figures according to race are not yet available for the class of 1975, it is likely that minority group enrollment is equal to or greater than the currently known proportion of 17 percent for the class of 1974.[†]

More than half of recent graduates said they are either practicing in or considering practice in one of these underserved areas. Among 1965 graduates, 12.3 percent said that they are now practicing in urban ghettos and 28.8 percent in rural areas. The number of those practicing in ghettos might be slightly inflated by a few in residency in urban teaching hospitals. It is not possible to compare these data to information about location of all practicing physicians, since no such information currently exists.

Summary of Trends

By observing which attitudes held by medical students are likely to be most enduring, we have constructed a tentative portrait of the next medical generation.

The "new physician" will be inclined to practice in a group setting, often relying on the help of a physician's assistant. He will probably be more anxious to see that the quality of medical care is assured through peer review, or perhaps to delegate the task to others if circumstances warrant. He will support relicensure and may be more willing to discipline peers who fail to meet standards of good care.

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[*] California Medical Association, Bureau of Research and Planning: Characteristics and Distribution of Physicians in California, June-July 1969

[†] California Medical Association, Bureau of Research and Planning: Socioeconomic Report—First year medical students in California and the United States. Vol. XI, No. 6:June 1971

In addition to working closely with peers toward higher professional standards, tomorrow's physician will more willingly accept involvement of government and other agencies in the broad system of health care. If he acts according to stated attitudes, he will become actively involved in developing comprehensive health plans for the community.

He appears likely to cooperate in restructuring the health care delivery system and will probably support some kind of national health insurance.

But while the new physician will cooperate more willingly with other health professionals, he values his personal role too highly to become an impersonal member of a bureaucratic system. He would rather be engaged in direct primary care than a technical specialty; and even if he specializes, he will probably consider himself more of a personal practitioner than a technician. He wants to know and deal with patients as a whole, rather than only with specific illnesses.

Since young physicians seem attracted to rural rather than urban areas, many are likely to set up practice in small communities even in isolated areas.

The new generation of physicians wishes to concern itself with the social and environmental causes of illness, and will want these fields emphasized in the education of all physicians.

Since they are currently skeptical about the ability of existing institutions to create needed changes, the members of this generation may be more receptive to experimental approaches and to the creation of different mechanisms to provide medical care. They may show some continuing unrest and unwillingness to work within the medical establishment unless given some voice in the decision-making process.

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

Billings, James Henry, Beverly Hills. Died March 3, 1973 in Los Angeles of cerebral hemorrhage, aged 62. Graduate of the University of Illinois College of Medicine, Chicago, 1942. Licensed in California in 1945. Doctor Billings was a member of the Los Angeles County Medical Association.

⁂

Buck, Irwin M., Beverly Hills. Died March 14, 1973 in Beverly Hills of pulmonary embolism, aged 57. Graduate of New York University College of Medicine, New York, 1940. Licensed in California in 1946. Doctor Buck was a member of the Los Angeles County Medical Association.

⁂

Buckwald, Albert Irving, San Jose. Died April 30, 1973 in San Jose, aged 51. Graduate of the Medical College of Georgia, Atlanta, 1945. Licensed in California in 1948. Doctor Buckwald was a member of the Santa Clara County Medical Society.

⁂

Bunch, Claude Carlston, Lodi. Died May 3, 1973 in Lodi, aged 80. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1932. Licensed in California in 1934. Doctor Bunch was a member of the San Joaquin County Medical Society.

⁂

Clinco, Arthur A., Los Angeles. Died May 6, 1973 in Los Angeles, aged 62. Graduate of Long Island College of Medicine, 1933. Licensed in California in 1943. Doctor Clinco was a member of the Los Angeles County Medical Association.

⁂

Curry, Clarence, Jr., Brawley. Died in April, 1973 in Alpine, aged 42. Graduate of the Creighton University School of Medicine, Omaha, 1957. Licensed in California in 1959. Doctor Curry was a member of the San Diego County Medical Society.

⁂

Drew, Herbert L., Chula Vista. Died May 6, 1973 in Chula Vista, aged 63. Graduate of McGill University Faculty of Medicine, Montreal, 1945. Licensed in California in 1946. Doctor Drew was a member of the San Diego County Medical Society.

Eagan, John C., Los Angeles. Died January 22, 1973 of myocardial infarction, aged 61. Graduate of the Creighton University School of Medicine, Omaha, 1934. Licensed in California in 1942. Doctor Eagan was a member of the Los Angeles County Medical Association.

⁂

Edson, David E., San Jose. Died May 10, 1973 in Palo Alto, aged 38. Graduate of Stanford University School of Medicine, Palo Alto, 1961. Licensed in California in 1965. Doctor Edson was a member of the Santa Clara County Medical Society.

⁂

Eisner, Cyrus I., Los Angeles. Died April 3, 1973 in Los Angeles of heart disease, aged 65. Graduate of Long Island College of Medicine, 1936. Licensed in California in 1946. Doctor Eisner was a member of the Los Angeles County Medical Association.

⁂

Graham, Glenn G., Burbank. Died April 19, 1973, in Burbank of cancer of the pancreas, stomach and colon, aged 68. Graduate of the University of Pittsburgh School of Medicine, 1935. Licensed in California in 1946. Doctor Graham was a member of the Los Angeles County Medical Association.

⁂

Granat, Henry George, Citrus Heights. Died January 15, 1973, aged 76. Graduate of the University of Manitoba Faculty of Medicine, Winnipeg, 1929. Licensed in California in 1937. Doctor Granat was a member of the Sacramento County Medical Association.

⁂

Halbach, Robert McC., Stockton. Died March 25, 1973, aged 79. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1920. Licensed in California in 1947. Doctor Halbach was a retired member of the San Joaquin County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

Harris, Charles P., Baywood Park. Died May 23, 1973 in San Luis Obispo, aged 66. Graduate of Eclectic Medical College, Cincinnati, 1935. Licensed in California in 1945. Doctor Harris was a member of the Fresno County Medical Society.

⁂

Hebert, William Morrison, Stockton. Died May 15, 1973 in Stockton, aged 50. Graduate of Washington University School of Medicine, St. Louis, 1950. Licensed in California in 1951. Doctor Hebert was a member of the San Joaquin County Medical Society.

⁂

Huntley, Eugene W., Ontario. Died April 21, 1973 in Duarte of cancer, aged 56. Graduate of the University of Southern California School of Medicine, Los Angeles, 1943. Licensed in California in 1948. Doctor Huntley was a member of the San Bernardino County Medical Society.

⁂

INGRAM, WILLIAM A., Oakland. Died May 9, 1973 in Auburn of ruptured berry aneurysm, aged 46. Graduate of the University of Nebraska College of Medicine, Omaha, 1953. Licensed in California in 1956. Doctor Ingram was a member of the Alameda-Contra Costa Medical Association.

⁂

JAKOBOVITS, RAFAEL, San Francisco. Died May 28, 1973 in San Francisco, aged 65. Graduate of Medizinische Fakultät der Universität, Wien, 1933. Licensed in California in 1942. Doctor Jakobovits was a member of the San Francisco Medical Society.

⁂

JOHNSON, BLAINE LEROY, Paradise. Died January 4, 1973 in Palo Alto of bronchopneumonia, aged 40. Graduate of St. Louis University School of Medicine, 1966. Licensed in California in 1967. Doctor Johnson was a member of the Butte-Glenn Medical Society.

⁂

JOHNSTON, FRANK R., Oakland. Died December 20, 1972 of bronchopneumonia, aged 78. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1923. Licensed in California in 1923. Doctor Johnston was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

JONES, MILTON RANDLE, SR., Claremont. Died January 25, 1973 of myocardial infarction, aged 66. Graduate of the University of California Medical School, Berkeley-San Francisco, 1933. Licensed in California in 1933. Doctor Jones was a member of the Los Angeles County Medical Association.

⁂

MAYER, HARRY J., Los Angeles. Died October 15, 1972, aged 75. Graduate of Rush Medical College, Chicago, 1924. Licensed in California in 1924. Doctor Mayer was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

MCINTYRE, CHARLES H., Cathedral City. Died April 25, 1973 in Cathedral City of carcinoma of the lung, aged 64. Graduate of the University of Michigan Medical School, Ann Arbor, 1931. Licensed in California in 1947. Doctor McIntyre was an associate member of the Monterey County Medical Society.

⁂

MCKEEVER, FRANCIS M., Los Angeles. Died March 31, 1973 in Los Angeles of corpulmonale, aged 71. Graduate of the University of California Medical School, Berkeley-San Francisco, 1927. Licensed in California in 1927. Doctor McKeever was a member of the Los Angeles County Medical Association.

⁂

NORWOOD, GEORGE E., Newport Beach. Died January 16, 1973 of cerebral arteriosclerosis, aged 68. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1932. Licensed in California in 1933. Doctor Norwood was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

PECK, RICHARD OLIVER, San Diego. Died April 29, 1973, aged 59. Graduate of the University of Southern California School of Medicine, 1940. Licensed in California in 1940. Doctor Peck was a member of the San Diego County Medical Society.

⁂

SHAW, WILLIAM F., San Francisco. Died May 5, 1973, aged 94. Graduate of New York University School of Medicine, New York, 1904. Licensed in California in 1914. Doctor Shaw was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

STOFER, DAR D., Monterey. Died May 7, 1973 in Carmel, aged 78. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1919. Licensed in California in 1942. Doctor Stofer was a member of the Monterey County Medical Society.

⁂

TALLEY, WILLIAM CLINTON, San Diego. Died January 19, 1973 of cancer, aged 44. Graduate of Duke University School of Medicine, Durham, 1954. Licensed in California in 1959. Doctor Talley was a member of the San Diego County Medical Society.

⁂

WARNOCK, ARCHIBALD W., Pasadena. Died April 17, 1973 in Pasadena, aged 78. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1923. Licensed in California in 1923. Doctor Warnock was a member of the Los Angeles County Medical Association.

⁂

WEAVER, PHILLIP TENNANT, Manhattan Beach. Died April 13, 1973 of heart disease, aged 51. Graduate of the University of Southern California School of Medicine, Los Angeles, 1946. Licensed in California in 1947. Doctor Weaver was a member of the Los Angeles County Medical Association.

⁂

WHEELER, OMER WILLIAM, Riverside. Died May 17, 1973 in Riverside, aged 65. Graduate of Temple University School of Medicine, Philadelphia, 1932. Licensed in California in 1935. Doctor Wheeler was a past president of the California Medical Association and a member of the Riverside County Medical Association.

Refer to: Fishbach RS, Rosenblatt JE, Dahlgren JG: Pyogenic vertebral osteomyelitis in heroin addicts. Calif Med 119: 1-4, Aug 1973

California Medicine
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Pyogenic Vertebral Osteomyelitis in Heroin Addicts

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JON E. ROSENBLATT, MD
JAMES G. DAHLGREN, MD
Los Angeles

The diagnosis of pyogenic vertebral osteomyelitis was made in seven narcotic addicts between 1967 and 1972. Vertebrae involved were either cervical or lumbar. Bacteriologic diagnosis was made in each case by percutaneous needle biopsy and aspiration. Staphylococcus aureus was cultured in two patients. Five patients had infections due to Gram-negative bacteria, including Klebsiella pneumoniae, Pseudomonas aeruginosa and Enterobacter. All patients were cured by treatment with antibiotics and immobilization.

NARCOTIC ADDICTS are subject to multiple medical complications, especially those related to the hematogenous dissemination of intravenously injected contaminated material. Despite frequent involvement of other organs, pyogenic osteomyelitis of the vertebral column has seldom been described[1,2] In the last five years we have seen seven cases of pyogenic vertebral osteomyelitis in users of intravenous drugs. Our experience suggests that this problem is more common than is appreciated and is actually increasing in incidence.

Patients

Seven patients with pyogenic vertebral osteomyelitis were seen at the UCLA Hospital and Wadsworth Veterans Administration Hospital between 1967 and 1972. Each patient was a user of intravenous heroin who presented with progressive neck or back pain. Duration of symptoms until admission ranged from ten days to seven months. A history of local trauma (five patients) and a short febrile course early in the illness (four patients) were each frequently noted. Before admission, all patients had been unsuccessfully treated with a variety of local supportive measures, including analgesics, muscle relaxants, bed rest and traction. Radiographic evaluation of the spine had been performed at least once on all patients, with negative results. On admission most patients were afebrile or had a low grade fever. Local tenderness of the involved vertebrae was elicited on palpation of the spine. Routine laboratory evaluation and blood cultures were performed. If, on admission, regular radiographs of the spine were negative, laminograms were performed. Radiographic evidence of osteomyelitis was demonstrated in all cases. Each patient underwent a percutaneous needle biopsy of the involved vertebra or disc space. The material obtained was cultured and yielded significant bac-

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Submitted November 27, 1972.

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teria in all patients. Antibiotics were administered on the basis of sensitivity testing of the organisms isolated. Patients were treated for four to six weeks with antibiotics and immobilization, which were continued until the patients demonstrated radiographic signs of stabilization.

Illustrative Case Histories

Case 2. A 24-year-old white man who used heroin and methedrine intravenously was admitted with a history of low back pain of ten days' duration following an automobile accident. Intermittent fever began four days before admittance. The temperature was 38.9°C (102°F) and on physical examination needle puncture marks were noted on both forearms and there was mild tenderness extending from the fifth lumbar and first sacral vertebrae to the left costovertebral angle. Leukocytes numbered 14,700 per cu mm and the erythrocyte sedimentation rate (ESR) was 32 mm in one hour. Routine lumbar-sacral spine films were negative. Blood cultures revealed Klebsiella pneumoniae and Enterobacter (species not determined) on separate occasions. Endocarditis was suspected and he was begun on cephalothin. Because of persisting severe low back pain, laminograms of the spine were performed and revealed narrowing of the disc space between the fifth lumbar and first sacral vertebrae with erosion of the adjoining vertebral bodies. A percutaneous biopsy of the disc space revealed both Klebsiella pneumoniae and Enterobacter on culture. The patient was treated in the hospital with gentamicin for one month and a back brace was fitted. Chloramphenicol was given by mouth for two months, at which time there was radiographic evidence of bone sclerosis with narrowing of the interspace.

Case 7. A 42-year-old Negro man had had neck pain for seven months before admission. He had been a regular user of intravenous heroin for 30 years. He had been admitted to another hospital after several weeks of increasing pain and fever. Radiographs taken there were negative and he was treated with analgesics and traction. The pain persisted after discharge and two months later he was admitted to a different hospital. Radiographs at that time reportedly showed collapse of the fourth cervical vertebra. He was treated with traction and neck support and was then discharged with a neck brace. Because of continuing pain, he was referred to our hospital for laminectomy. On admission, the patient was afebrile. There was tenderness over the lower part of the neck with pronounced decrease in range of motion in all directions. Hypesthesia was noted over the medial aspect of the left arm and ulnar part of the left hand. Leukocytes numbered 6,100 per cu mm and the ESR was 17 mm in one hour. X-ray films on admission showed collapse of the fourth cervical vertebra with narrowing of the interspaces between the third and fourth and the fourth and the fifth vertebrae. Irregularity of the bodies of the third, fourth and fifth vertebrae were noted, which on laminography was seen consistent with severe osteomyelitis. Percutaneous needle biopsy was performed. Culture of the material grew Staphylococcus aureus. Because the Gram stain of the aspirate suggested the presence of anaerobic bacteria as well as S. aureus, the patient was initially treated with clindamycin, 300 mg orally every six hours. When all culture material was finally evaluated and no anaerobic organisms were isolated, therapy was changed to dicloxacillin, 500 mg orally every six hours. The patient was also fitted with a Minerva jacket. At last report he was under therapy and doing well.

Results

Data on the seven patients are summarized in Table 1. Five of the seven were seen between 1971 and 1972. The age range was from 17 to 42 years, the average 28 years. There were six males and one female. In most patients the leukocyte count was within normal limits and in no case did it reach 15,000 per cu mm. The average was 9,350 per cu mm. The erythrocyte sedimentation rate was uniformly elevated, ranging between 17 mm and 39 mm in one hour with an average of 30 mm. Vertebral lesions were primarily cervical (two cases) or lumbar (five cases), with a tendency for involvement of the lower portions of each region. In Case 2 there was involvement of the fifth lumbar to the first sacral vertebrae. In five patients, osteomyelitis involved two vertebral bodies as well as the adjacent disc space. Only the body of the first lumbar vertebra was affected in Case 4, and there was involvement of three vertebrae with two disc spaces in Case 7. Staphylococcus aureus was isolated in two patients. Pseudomonas aeruginosa, Klebsiella pneumoniae and Enterobacter (species not determined) were each isolated twice (Patient 1 was infected with both Klebsiella and Enterobacter). Blood cultures revealed the same organisms as those observed on biopsy in Cases 2 and 4. In four patients the main therapy was four to six weeks of gentamicin. The

TABLE 1.—*Clinical Data in Seven Cases of Pyogenic Vertebral Osteomyelitis in Heroin Users*

				Admission laboratory data			Culture results		
Patient	*Age*	*Sex*	*Year of Admission*	*White cell count (per mm³)*	*Sedimentation rate (mm/hr)*	*Vertebrae involved*	*Needle biopsy*	*Blood*	*Antibiotic treatment*
1	17	M	1968	6,350	32	L_2-L_3	Pseudomonas aeruginosa	....	Gentamicin
2	24	M	1970	14,700	36	L_5-S_1	Klebsiella pneumoniae, Enterobacter	Klebsiella pneumoniae, Enterobacter	Gentamicin →Chloramphenicol
3	26	M	1971	5,800	20	C_5-C_6	Enterobacter	....	Tetracycline
4	36	M	1971	12,000	31	L_5	Staphylococcus aureus	Staphylococcus aureus	Methicillin
5	25	M	1971	10,800	35	L_1-L_2	Klebsiella pneumoniae	....	Gentamicin →Tetracycline
6	25	F	1972	9,700	39	L_3-L_4	Pseudomonas aeruginosa	....	Gentamicin Carbenicillin
7	42	M	1972	6,100	17	C_3-C_5	Staphylococcus aureus	....	Clindamycin → Dicloxacillin

average dose was 1.5 mg per kg of body weight intramuscularly every eight hours. No evidence of toxicity was noted. Carbenicillin (24 grams intravenously per day) and gentamicin in combination were used in Case 6 after *in vitro* synergism was demonstrated. Tetracycline, methicillin and clindamycin were the primary therapy in one case each. Six patients were cured of infection, judging by symptomatic response, fall in sedimentation rate and evidence of radiographic healing of the involved vertebrae. The patient in Case 7 is still being treated, but has had considerable symptomatic improvement.

Discussion

Staphylococcus aureus has been considered the most frequent etiologic agent in osteomyelitis of the spine.[3-5] However, it appears that in heroin addicts Gram-negative bacteria are the most common cause of pyogenic vertebral osteomyelitis. The five cases recently reported by Lewis et al[2] were all due to Pseudomonas aeruginosa. In addition, Holzman and Bishko described three cases caused by Pseudomonas, by Candida stellatoidea, and by both Pseudomonas and Staphylococcus aureus.[1] Of our seven patients, only two were infected with Staphylococcus aureus; the other five cases were due to Gram-negative bacteria (Pseudomonas, Klebsiella, Enterobacter). We have recently noted a similar predominance of Gram-negative bacteria in endocarditis in heroin addicts.[6] The origin of these bacteria is unclear. Addicts are often admitted to hospital because of complications of drug use, and frequently they receive antibiotics. Their skin may thereby become colonized by nosocomial Gram-negative bacteria which may then enter the blood stream when narcotics are injected. It is also possible that the drugs themselves are contaminated during dilution and distribution.

Specimens for culture from our seven cases were obtained by percutaneous needle biopsy and aspiration of the intervertebral space. This procedure, performed under local anesthesia with fluoroscopic control, caused minimum discomfort and no complications. It should be the procedure of choice for obtaining culture material from sites of pyogenic vertebral osteomyelitis. The specimen obtained will frequently not be grossly purulent and it may even be necessary to wash the area with normal saline solution to obtain material appropriate for culture. However, even in these situations, cultures will yield significant pathogenic organisms.

Five of our patients gave a history of trauma preceding the development of symptoms. This antecedent has been noted by other observers.[7,8] McLaurin suggested that trauma may provide a susceptible site for the implantation of bacteria.[9] The lower cervical and lumbar vertebrae are the most common sites of adult hematogenous osteomyelitis and these are also the most mobile parts of the spine[10] and the most likely to be involved in minor trauma.

The slowly progressive indolent nature of this disease, the long delay in making the diagnosis, the absence of fever, the low white blood cell count and elevated erythrocyte sedimentation rate have all been previously noted.[4,5,8,9,11] Because routine radiographs may be normal, it is often necessary to perform laminograms. If all radiographs are negative and symptoms persist, studies should be repeated after a short interval because of the delayed radiographic appearance of bone lesions in osteomyelitis.

Because of the wide variety of pathogens which may be involved in this disease, therapy must be based on the sensitivity of the specific organism isolated. In osteomyelitis due to Gram-negative bacteria, a bactericidal antimicrobial agent should be used whenever possible. The Gram-positive organisms encountered in these infections are frequently resistant to many antimicrobial agents, including the few clinically-useful bactericidal agents. In our experience, gentamicin appears to be the drug of choice for therapy of vertebral osteomyelitis due to these resistant bacteria. A combination of gentamicin and carbenicillin may provide enhanced activity against Pseudomonas aeruginosa as well as Serratia marcescens, an organism not encountered in our patients. Tetracycline was used as primary antimicrobial therapy in one patient infected with Enterobacter, resistant to most other agents. It was also used in another patient for continued oral therapy after discontinuation of gentamicin. Both patients had good clinical response.

It is likely that the increasing use of illicit intravenous drugs administered by unsterile methods will result in an increased incidence of pyogenic vertebral osteomyelitis. Five of our seven cases were seen in 1971-1972, suggesting that this increase is already occurring. Our data indicate that a user of intravenous drugs who presents with neck or back pain should be considered to have vertebral osteomyelitis until proven otherwise.

ADDENDUM

Since this report was written we have seen two additional patients: One was a 45-year-old man admitted with oteomyelitis of the eighth to eleventh thoracic vertebrae due to Serratia marcescens. He is improving on gentamicin therapy. The second patient, a 40-year-old man with osteomyelitis of the third and fourth lumbar vertebrae due to Pseudomonas aeruginosa, is currently under therapy with tobramycin.

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Refer to: Klock JC, Sexton MJ: Rhabdomyolysis and acute myoglobinuric renal failure following heroin use. Calif Med 119:5-8, Aug 1973

Rhabdomyolysis and Acute Myoglobinuric Renal Failure Following Heroin Use

JOHN C. KLOCK, MD, and MICHAEL J. SEXTON, MD, *San Francisco*

RHABDOMYOLYSIS IS USUALLY CONSIDERED a rare phenomenon and most medical textbooks devote little space to describing it. However, recently several observers[1-5] have pointed out that it occurs probably more frequently than is generally appreciated. Recently Richter et al[6] described heroin-induced rhabdomyolysis and myoglobinuria in four addicts, a previously unrecognized association. It is the purpose of this report to present two more cases of heroin-induced rhabdomyolysis and discuss its cause and classification as a myoglobinuric syndrome.

Reports of Cases

CASE 1. A previously healthy 20-year-old college student entered the hospital because of an unusual reaction to an injection of heroin. On the evening before admission, he had intravenously injected a drug thought to be heroin, and thereupon became sweaty, nauseated, vomited and fell asleep sitting in a chair. Six hours later he awoke with tinnitus, generalized weakness, and pain in the lower back and right hip. He noticed that his urine was dark brown and came to the emergency room.

On admission to the hospital, the patient was alert and cooperative and in no obvious distress. The blood pressure was 130/80 mm of mercury, the pulse 68 beats per minute, respirations 18 per minute and temperature 37.1°C (98.8°F). Physical examination, with the exception of subjective muscle tenderness in the posterior thighs, the buttocks and the lower back, and generalized muscle weakness, was entirely normal. The neurologic examination revealed no evidence of focal sensory or motor deficit.

The packed cell volume was 58 percent of the whole blood, with clear plasma, hemoglobin 19 grams per 100 ml, and white blood cell count 17,500 per cu mm with 75 percent neutrophils, 14 percent bands, 5 percent lymphocytes and 6 percent monocytes. Serum sodium was 135 mEq, potassium 7.0 mEq, chloride 107 mEq, bicarbonate 24 mEq per liter. Blood urea nitrogen was 31 mg and creatinine 2.6 mg per 100 ml, glutamic oxaloacetic transaminase 90 international units per liter, aldolase 21.2 milliunits per ml (normal adult 3 to 10). Creatine phosphokinase on days 1, 2 and 3

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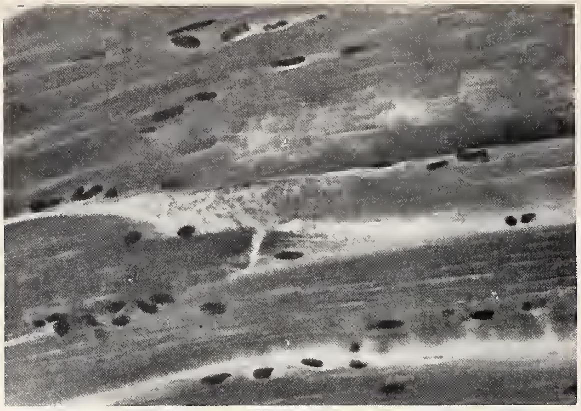

Figure 1.—Biopsy specimen from painful right gluteus muscle (Case 1) showing granular degeneration of muscle fibers. (Hematoxylin and eosin, original X 250.)

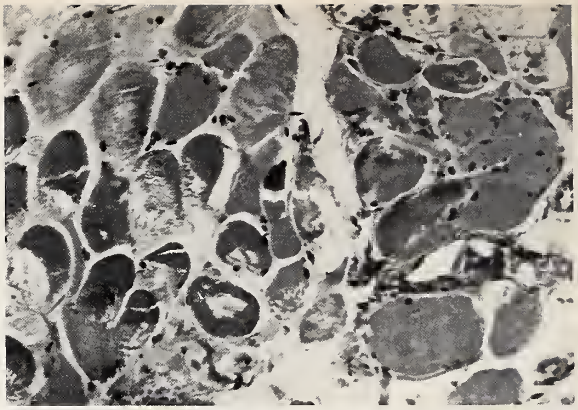

Figure 2.—Biopsy specimen from clinically uninvolved muscle, right quadriceps (Case 1) showing fragmentation of muscle fibers with central nuclei and an inflammatory infiltrate. (Hematoxylin and eosin, original X 250.)

was 36,000, 64,000 and 39,000 IU per liter, with only skeletal muscle fractions present on isoenzyme analysis. Random glucose, total bilirubin, alkaline phosphatase, calcium, phosphorus, whole blood pH and arterial blood gases were within normal limits. The urine was dark brown with a pH of 5, four plus reaction for blood and protein, two plus for glucose and negative for acetone and bilirubin. The urinary sediment contained many hyaline and coarsely granular casts, two to four white blood cells per high dry field and no red blood cells or red blood cell casts. Urine myoglobin by both ultrafiltration and electrophoretic techniques was positive. Urine toxicology was negative for alcohols, heavy metals, ethylene glycol and neutral and alkaline drugs including quinine, and was positive for morphine. A cigarette filter that the patient had used to strain the heroin he had injected was obtained and analyzed. The results showed only the presence of morphine and trace amounts of nickel, iron and nicotine.

The patient was oliguric, hyperkalemic and in obvious acute renal failure. The diagnosis of rhabdomyolysis and myoglobinuric renal failure was made and therapy with insulin, glucose, bicarbonate and oral sodium polystyrene sulfonate (Kayexalate®) was begun immediately. When there was no response to the rapid intravenous infusion of three liters of saline solution, 25 grams of mannitol was given intravenously and a rapid and sustained diuresis followed. The subsequent treatment course was uncomplicated and the patient completely recovered.

Muscle biopsy specimens from two separate sites were obtained on the third hospital day. The first specimen was obtained from a tender site on the patient's right hip (Figure 1), the second from a non-tender area on the right leg (Figure 2). Both specimens showed scattered areas of necrosis, variation in fiber size, edema and degeneration of muscle fibers. The process was focal, with some areas of normal muscle. However, the changes in the second specimen were more pronounced than those in the clinically more severely affected muscle. The patient was discharged on the fifth hospital day and remained well in a four-month follow-up.

CASE 2. A 30-year-old man who had never previously used drugs entered the hospital with a painful, swollen right arm and acute renal failure. Two days previously he had injected into his right antecubital vein a substance thought to be heroin. Immediately afterward he noted severe pain in the right arm and shoulder. Painful swelling of the right arm, generalized weakness and the passing of dark urine prompted him to visit an emergency room, where he was found to have signs of acute morphinism; systemic vasculitis was diagnosed and he was referred on the following day to San Francisco General Hospital.

Upon arrival, the patient was drowsy but oriented and cooperative. The blood pressure was 130/90 mm of mercury, the pulse 100 per minute, respirations 16 per minute and temperature 37.9°C (100.2°F). Except for a painful, erythematous, swollen right arm, hand and shoulder, no abnormalities were noted on physical examination. Sensory and motor function were normal.

Packed cell volume was 51.5 percent of whole blood. The plasma was clear. Hemoglobin was

16 grams per 100 ml, and the leukocyte count was 24,300 per cu mm with 56 percent neutrophils, 38 percent bands, 2 percent metamyelocytes, 1 percent myelocytes, 2 percent lymphocytes and 1 percent monocytes. Serum potassium was 8.8 mEq per liter. Blood urea nitrogen 40 mg, creatinine 5.7 mg, calcium 6.5 mg, phosphorus 7.1 mg, and magnesium 3.4 mg per 100 ml. Glutamic oxaloacetic transaminase was 1,020 IU, aldolase 760 S-L units (normal adult 3 to 8), creatine phosphokinase 38,300 IU and lactic dehydrogenase 2,905 IU per liter. Two antinuclear antibody assays were negative, and there were normal values for serum sodium, bicarbonate, chloride, bilirubin and random glucose. The urine was dark brown, with a specific gravity of 1.026, pH 5, two plus reaction for protein and glucose, four plus for blood, and negative reaction for acetone and bilirubin. The urinary sediment contained many pigmented granular casts and no white blood cells, red blood cells or red blood cell casts. Urine toxicology was negative for alcohols, neutral and alkaline drugs, heavy metals and quinine and positive for morphine. Urinary myoglobin was not determined. A spoon in which the heroin mixture had been heated was analyzed and the results showed only the presence of opiates with no evidence of quinine or other adulterants. The patient was oliguric and in acute renal failure. Immediate treatment with intravenous fluids, mannitol and furosemide had no effect. Treatment with glucose insulin, bicarbonate, oral sodium polystyrene sulfonate and peritoneal dialysis were begun but the patient remained oliguric. Supportive treatment including a two-week course of hemodialysis resulted in full recovery of renal function. The development of neurologic deficit in the right hand necessitated fasciotomy on the third hospital day. The patient made uneventful recovery and was discharged on the 50th hospital day with some residual sensory and motor loss in the right arm.

Discussion

Rhabdomyolysis, or skeletal muscle necrosis, associated with the use of heroin is pathologically similar to rhabdomyolysis of any other cause. Muscle biopsy in such cases presents a spectrum of changes ranging from structural alterations of fibers without necrosis to severe necrosis of all muscle fibers, edema and focal hemorrhage. Substances released from affected tissues, among them myoglobin, are thought to be responsible for the clinical syndrome and pathological consequences of rhabdomyolysis.

The presence of a guaiac-positive pigment in urine which contains no erythrocytes in a patient with muscle pain, weakness and normal-colored serum in pathognomonic of myoglobinuric rhabdomyolysis.[1] Patients with this syndrome usually also have fever, leukocytosis, pyuria, hyperkalemia, granular cylindruria, a high ratio of creatinine to blood urea nitrogen, and elevation of serum glutamic oxaloacetic transaminase, lactic dehydrogenase, creatine phosphokinase and succinic dehydrogenase. The detection of myoglobin in the urine and a muscle biopsy confirm the diagnosis, although myoglobinuria is not always associated with light microscopic changes and a normal biopsy does not exclude the diagnosis.

Acute renal failure is the most serious complication of rhabdomyolysis and is the most common cause of death.[1] It is an inconstant feature of the disease and is not always related to the degree of muscle damage, other factors such as systemic acidosis, hypovolemia and dehydration often contributing to its development. Acute elevation of toxic substances released from damaged tissues or hyperkalemia may also cause death, often suddenly. Neurocirculatory embarrassment of affected limbs from severe myoedema remains the most significant cause of morbidity in surviving patients and may necessitate fasciotomy.

The treatment of the acute rhabdomyolysis syndrome is directed toward the prevention of acute renal failure and the complications of severe myoedema. The first can best be done by early recognition and the use of diuretics in most instances. Peritoneal dialysis and hemodialysis may be needed in those patients not responding to diuretics and should be used when necessary. Immediate fasciotomy in patients with severe muscle swelling or at the first sign of neurovascular insufficiency may help in the prevention of permanent neurologic damage[6,8] and should be used when appropriate.

The cause of rhabdomyolysis following heroin use remains obscure. It may recur in some persons[6] suggesting an individual propensity for its development, as is seen in exercise-induced rhabdomyolysis.[3] Recently Penn and Rowland[2] emphasized the role of coma and prolonged immobilization in the production of this syndrome. Schreiber et al[7] reported a similar crush syndrome in comatose patients following heroin use. However, heroin adulterant was suggested as the incriminating element in the four patients reported by Richter.[6] Heroin's role in the production of rhabdomyolysis in our patients cannot be fully explained. As far as can be determined, intraarterial injection did not take place and we are unable to say whether heroin was directly responsible for the muscle necrosis observed in either case. An idiosyncratic reaction to apparently unadulterated heroin or an unusual susceptibility of the patients seems likely, although the more common role of crush injury seen in most cases of rhabdomyolysis following drug use is recognized and cannot be excluded as a contributing element in Case 1.

Summary

Rhabdomyolysis following heroin use was demonstrated in two non-addicted persons. Evidence is provided that there may be generalized involvement of muscle and that the crush factor may not be related to the production of rhabdomyolysis in all patients with this syndrome. It is suggested that heroin is only one of many agents capable of producing rhabdomyolysis in susceptible persons and that individual susceptibility may play a major role in the disease. Finally, emphasis should be placed on the early recognition and appropriate management of this syndrome, the complications of which are largely preventable.

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Refer to: Chater N, Mani J, Tonnemacher K: Superficial temporal artery bypass in occlusive cerebral vascular disease. Calif Med 119:9-13, Aug 1973

Superficial Temporal Artery Bypass in Occlusive Cerebral Vascular Disease

In carefully selected cases, superficial temporal artery bypass appears to be a promising and useful method for bringing about an improved collateral supply in problems of occlusive cerebral vascular disease. Such a procedure appears to improve the quality of life.

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IT IS WELL RECOGNIZED that stroke is a leading cause of death and disability in the United States.[1,2] It is third in frequency after heart disease and cancer as a cause of suffering in this country.[1] Approximately 200,000 new strokes occur per year, and this statistic may be a conservative estimate.[2] Two million people in America are at present disabled and unemployable as a result of this disease process.[3] Two-thirds are under 65 and in the so-called pre-retirement or productive years.[4] After the onset of a fixed stroke, rehabilitation may be extremely difficult[5] and the cost (in loss of human productivity) has been estimated at three billion dollars a year excluding acute hospitalization.[3] The seriousness of the problem is therefore apparent.

Natural History of Cerebral Vascular Disease and Arteriographic Investigation

Patients who have transient ischemic attacks (TIA's) have an 18 to 60 percent chance of having a completed stroke within a year.[6-8] One of the aims of stroke therapy, therefore, is to prevent such a catastrophe and, if possible, to improve the quality of life.[2] In a series of 100 consecutive patients presenting with TIA's (or TIA's with a mild completed stroke), 33 percent of those studied by arteriography were found to have significant obstructive lesions classified as "inaccessible or inoperable" by general vascular techniques.[9,11] Arteriographic investigations from the National Cooperative Study revealed 6 percent of the patients had purely inaccessible surgical lesions and an additional 33 percent had inaccessible combined with accessible lesions, the so-called "tandem lesion."[10] This is to be expected, as cerebrovascular artherosclerotic disease is a multifocal process. Other arteriographic studies have found 33 percent of obstructive lesions to be intracranial.[19] An additional 5 to 8 percent of patients studied for cerebrovascular symptoms were shown to have old complete internal carotid occlusions, which, at present, are considered inoperable by vascular surgeons because of the poor success rate in reopening the vessel.[10,11] At the same time, vascular surgeons are loath to operate on an acute internal carotid occlusion for fear of precipitating a hemorrhagic infarct.[13] Thus, some 12 percent

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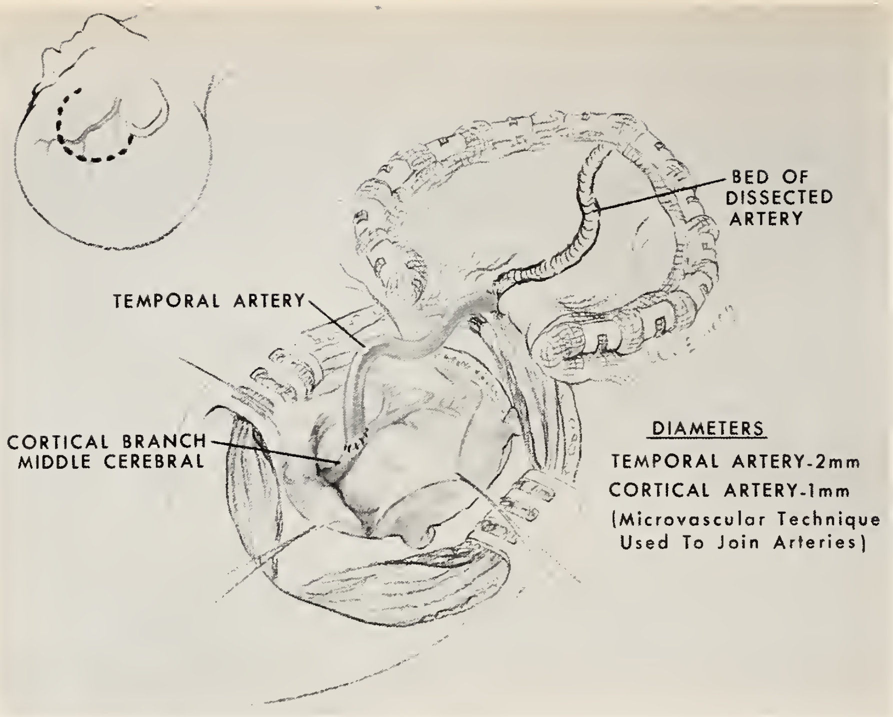

Figure 1. — Anastomosis, superficial temporal artery and branch of middle cerebral artery (collateral augmentation procedure).

of patients studied by arteriography may be found to have lesions that are "inoperable" by present conventional surgical techniques.[10,11] If the statistics are accurate, this potentially amounts to some 20,000 persons a year.

Surgical Procedure and Theoretical Considerations

For the bypass operation, the superficial temporal artery (average diameter 2 mm) is dissected free from the scalp and a burr hole or small craniectomy is fashioned of sufficient size to expose a suitable cortical artery, 1 mm in diameter or larger. Such arteries may now be found with high reliability.[14] An end-to-side anastomosis between the superficial temporal artery and the appropriate cortical artery is then performed with the operating microscope, using micro-instrumentation under 16 to 25 power magnification (Figure 1). The major obstruction may be bypassed in this manner[15,16] and an additional collateral blood supply provided for ischemic areas.[17,18] As "hemodynamic" cerebrovascular insufficiency symptoms are the result of insufficient collateral supply rather than the block itself,[19,20] such a surgical procedure may alleviate the symptoms and signs of cerebral ischemia.[17,19] Whether such a procedure can reverse pre-existing cerebrovascular neurological defects partially or completely is still open to considerable debate.[11,20] Some pathological studies have suggested, however, that at least minor deficits theoretically could be improved with the restoration of normal perfusion pressures to the areas of marginal flow.[21] At present there is no clinical method of determining in advance which neurons are nonfunctioning because of anoxia and which neurons are, in fact, dead. There is considerable experimental evidence, however, suggesting that neurons may live and tolerate anoxia without necrosis for considerable periods.[22]

Illustrative Cases

CASE 1. *Left Internal Carotid Occlusion and Right Carotid Siphon Stenosis with* TIA's

A 63-year-old, right-handed salesman was evaluated for recurrent attacks of left-sided numbness, weakness and dysarthria over a period of about six months. Twelve years previously he had had an attack of right-sided numbness and had completely recovered. Results of physical examination were within normal limits. Arteriograms revealed a complete left internal carotid occlusion with collateral supply through the ophthalmic system and 90 percent stenosis of the right carotid siphon. A right superficial temporal artery-cortical artery bypass was performed. The patient was asymptomatic thereafter and follow-up arteriograms six months later showed well functioning collateral vessels (Figure 2).

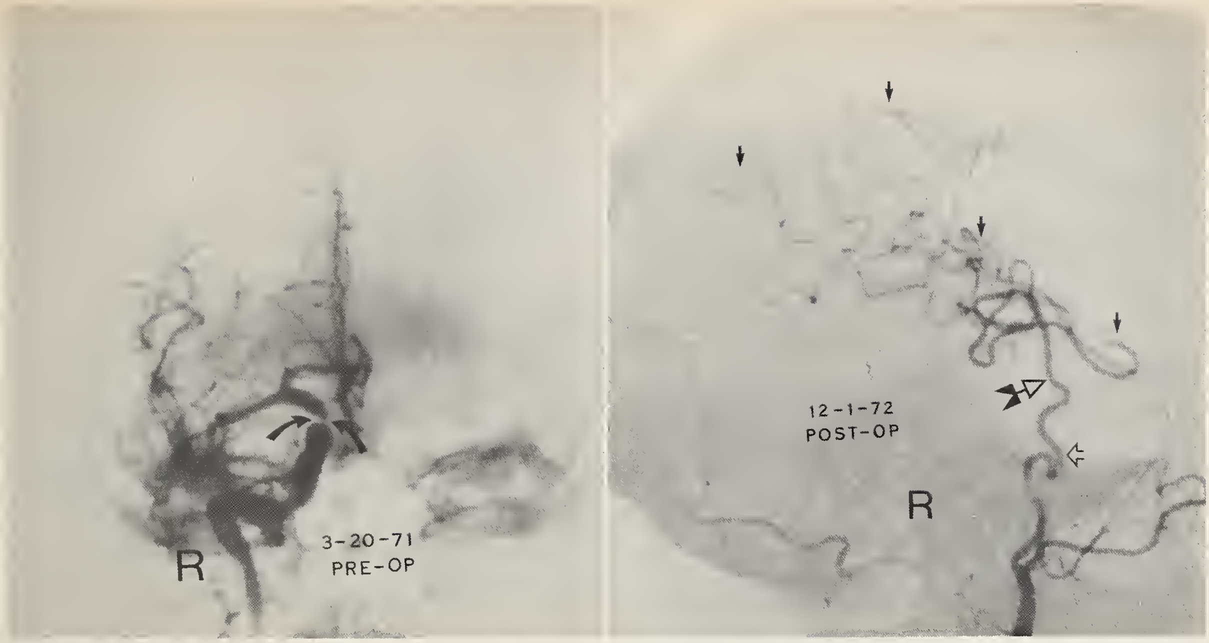

Figure 2.—**Left**, preoperative right common carotid arteriogram, antero-posterior view, showing severe carotid siphon stenosis (curved black arrows). **Right,** postoperative lateral view shows dilated superficial temporal artery (open arrow), point of anastomosis (black and white arrow), and middle cerebral artery filling (small black arrows).

CASE 2. *Left Middle Cerebral Stenosis with* TIA'*s*

A 64-year-old, retired, right-handed baker was investigated for two attacks of right-sided weakness, numbness and aphasia. Physical examination was unremarkable. Arteriograms showed 90 percent stenosis of the left middle cerebral artery with poor collateral vessels. Left superficial temporal artery-cortical artery anastomosis was performed. Postoperatively the patient remained asymptomatic. Follow-up arteriograms at six months showed a patent functioning anastomosis.

CASE 3. *Left Internal Carotid Artery Occlusion with* TIA'*s.*

A 59-year-old right-handed construction worker had quit working because of recurrent attacks of right-sided dysphasia, with numbness and weakness of the right arm and leg. Physical examination revealed moderate weakness of the right upper extremity and face with mild dysphasia and dysarthria. Arteriograms showed complete occlusion of the left internal carotid artery with poor collaterals from the left posterior communicating artery and right anterior communicating artery. Left superficial temporal-cortical artery anastomosis was carried out. The patient had no further attacks and on physical examination after the operation the right-sided weakness and dysphasia was minimal. Arteriograms four months after operation showed a patent anastomosis with good filling of the middle cerebral artery (Figure 3).

CASE 4. *Right Internal Carotid Artery Occlusion with Progressive Loss of Neurological Function*

A 54-year-old, Japanese clerk was admitted on suspicion of brain tumor because of progressive clumsiness over a period of two months, numbness and inability to distinguish objects in his left hand. On physical examination clumsiness of the left hand, decreased sensation to pinprick and severe astereognosis of the left upper extremity were noted. Arteriograms showed right internal carotid artery occlusion and precarious filling of collateral vessels through a small right posterior communicating artery. Right superficial temporal-parietal anastomosis was performed and a week later arteriograms showed a patent anastomosis with enlargement of the superficial temporal artery to approximately three time its preoperative diameter (Figure 4). In a short follow-up at the time of this report, astereognosis had diminished, as had sensory loss and clumsiness of the left hand.

CASE 5. *Left Internal Carotid Occlusion with Severe Cerebrovascular System Deficit*

A 44-year-old, right-handed, government agent had had two transient attacks of right-sided weakness and aphasia, with recovery, followed by an

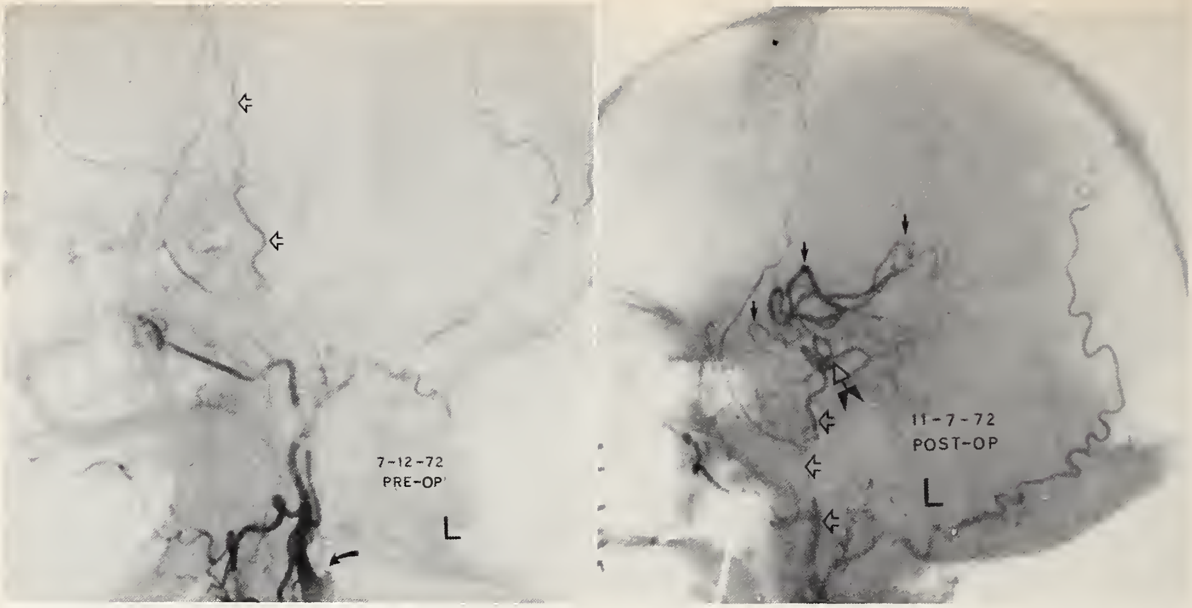

Figure 3.—Left, lateral view of preoperative left common carotid arteriogram showing complete occlusion of left internal carotid artery at the bifurcation (black curved arrow). The open arrows point to superficial temporal artery. **Right,** postoperative (four months) left external carotid arteriogram shows slight hypertrophy of left superficial temporal artery (open arrows), point of anastomosis (black and white arrow), and middle cerebral artery filling (black arrows).

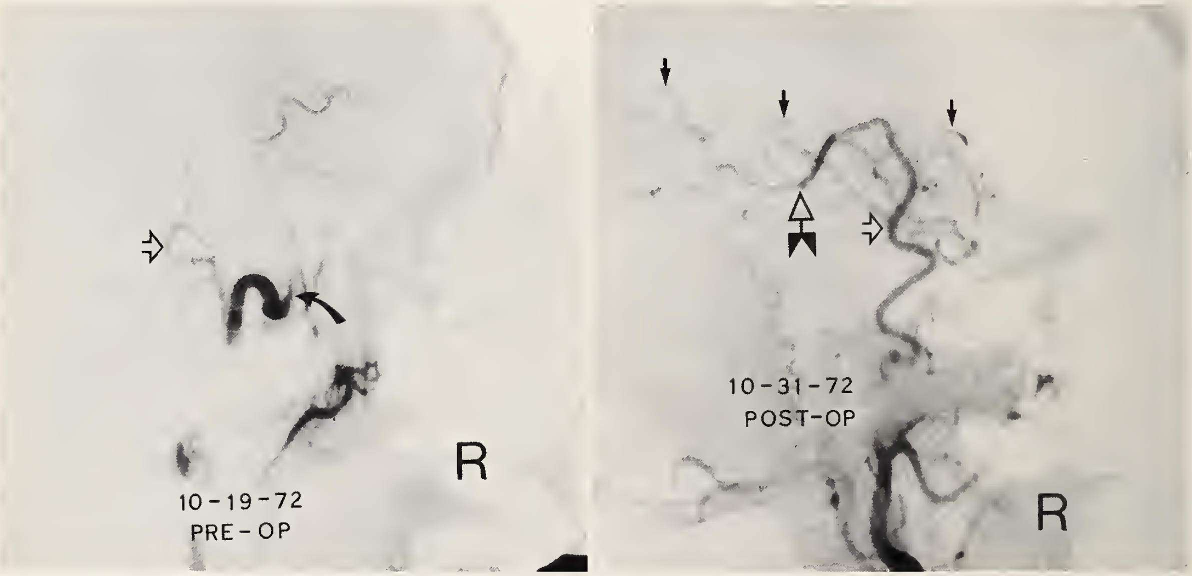

Figure 4.—Left, preoperative right common carotid arteriogram, lateral view, shows complete occlusion of right internal carotid artery at the carotid siphon (curved black arrow). Open arrow points to preoperative right superficial temporal artery. **Right,** right external carotid arteriogram, lateral view, one week postanastomosis of right superficial temporal artery and right middle cortical artery branch. Note the dilated right superficial temporal artery (open arrow). Point of anastomosis (black and white arrow). Small black arrows indicate filling of the right middle cerebral artery branches.

attack of complete right hemiplegia and aphasia. Complete motor aphasia and total flaccid right hemiparesis were noted on physical examination. Arteriograms revealed complete occlusion of the left internal carotid artery. Superficial temporal artery bypass was performed 20 days after onset of the severe deficit. Four months later the patient had residual very mild clumsiness of the right hand and minimal dysphasia. Doppler flow studies showed the anastomosis to be patent.

A post-operative arteriogram shows a patent, well-functioning anastomosis, with enlargement of the superficial temporal artery.

Discussion

Historically, the first two surgical procedures of this type (superficial temporal artery bypass) were performed for cerebro-vascular insufficiency almost simultaneously, one in Burlington, Vermont, (Donaghy) and one in Zurich, Switzerland (Yasargil) in late 1967.[23] The anastomosis site in the Zurich case continues to be open and enlarging, indicating that long term patency is possible. The patient has remained asymptomatic.[24]

Since 1967 about a hundred such procedures have been performed in the world. At the European Congress in Prague in 1971, reports on 44 temporal bypass operations and postoperative results were presented, and the patency rate was approximately 60 percent.[25] Of 28 such operations performed by Yasargil and reviewed by one of us (Chater) in 1971, the mortality rate was zero and the morbidity was very low. The patency rate of the anastomotic sites was 66 percent and was associated with a similar percentage of clinical improvement.[24] Twelve such operations have been performed at this hospital to date. In six cases in which postoperative arteriograms have been done the anastomosis is patent. Eight of the 12 patients have shown significant clinical improvement. One patient died a month after operation after acute bleeding from a chronic gastric ulcer. (Permission for autopsy was not obtained.) In three patients there has been no clinical change.

Indications

The tentative indications for such a collateral augmentation procedure may be outlined as follows:

1. *Multiple vessel occlusions associated with generalized low cerebral perfusion symptoms,* such as, mental deterioration and memory loss, vertigo, ataxia, and light-headedness.[26]

2. *Focal symptoms and signs resulting from inadequate regional perfusion.*

Types:

(a) Internal carotid artery occlusion with inadequate collaterals (Figures 3 and 4).

(b) Internal carotid artery siphon stenosis (inaccessible) with inadequate collaterals (Figure 2).

(c) Middle cerebral artery occlusion with inadequate collaterals and mild neurologic deficit.

(d) Middle cerebral artery stenosis with inadequate collaterals (Case 2 of series).

(e) Vertebral-basilar arterial stenotic lesions (inaccessible) with inadequate collaterals.

This collateral augmentation approach may also be useful in the therapy of non-atherosclerotic occlusive processes in the cerebrovascular systems, such as, arteritis.[27-31]

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Sexuality, Contraception and Pregnancy in a High-School Population

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Students in a middle-class and in an economically lower-class high school were surveyed regarding their attitudes and behavior with respect to sexuality, contraception, and pregnancy. A large majority of students approved of premarital intercourse for both sexes within the context of a loving relationship. The most important deterrent to sexual intercourse was fear of pregnancy. A majority of both sexes had had sexual intercourse. Forty percent of the sexually active had used no contraception on some occasions, and many of the remainder had used poor methods such as withdrawal or rhythm. The pregnancy rate was high—at least 20 percent in several of the sexually active subgroups.

Parents were an infrequent source of information about sex. On the other hand, there was some evidence that students exposed to a sex education program retained useful information if it was relevant to their situation, and if they were appropriately motivated.

A model for integrating the various aspects of this subject area is offered.

THE SEXUAL AND CONTRACEPTIVE BEHAVIOR of adolescents and their modes of coping with an unplanned pregnancy have increasingly become subjects of concern for contemporary physicians and the overall medical care system. This is appropriate because recent investigations have demonstrated that pre-marital heterosexual behavior has more acceptance and has been carried further by more people during the last decade.[1,2] In fact, the most current national survey revealed that almost one out of every two unmarried women have had sexual intercourse by the time they are 19.[2] However, while the incidence of advanced sexuality is at a high level in unmarried adolescence, related precautionary behavior which would guard against undesirable medical and social consequences has not reached a correspondingly high level.

The national survey revealed that 80 percent of the sexually active adolescent girls were not using contraception or were using it inefficiently and that distressingly large proportions of these adolescents were becoming pregnant.[3] Other sources indicate that large proportions of the women seeking therapeutic abortion throughout the nation are unmarried adolescents.[4] Finally, for those pregnant adolescents who do not seek abortion, it is well established that teenage child-bearing carries a far greater risk with regard to the health and social consequences.[5]

Physicians can help with these problems by developing their role as an important source of information and guidance for the sexually active teenager as well as for the parents of teenagers and of younger children soon to be teenagers. The majority of sexually active teenage women do not

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know what time during the menstrual cycle they are likely to get pregnant.[3] There is, also, a great need for information about contraceptive side-effects, venereal disease, sexual anatomy and physiology, and the medical and psychological consequences of abortion. The physician can help in providing this information and encouraging the individual or the family to talk through the issues and problems which come up in the context of acquiring this information. For these reasons, it is important for physicians to have knowledge about the current status of community behavior and value patterns with respect to adolescent sexuality, contraception, and pregnancy. To this end, I will present and discuss in the material below the results of a survey of attitudes and practices regarding sexuality, contraception and unplanned pregnancy among a population of suburban high-school students conducted in the Spring of 1971.

Method

A sexual attitude and practice questionnaire was developed and pre-tested with a small teenage population. It was then administered in two San Francisco Bay Area high schools—one predominantly white and middle-class as measured by economic standards, the other racially and ethnically mixed and lower-class. In each school one teacher administered the questionnaire to all of the junior and senior students in seven different classes on one selected day. The classes had been selected previously by each teacher as ones which included students representative of the range of capacities and interests within the school population. In this way a representative, although not a random sample was secured. In all classes students were informed of the survey several weeks ahead of time, were given the opportunity to discuss the purpose and nature of the study, and—as required by California law—were required to secure parental consent for their participation. During questionnaire administration there were five and nine refusals to participate in the study in the middle-class and lower-class schools respectively. During the classroom period, the questionnaire was completed anonymously by each student, who then sealed it in a stamped envelope which had the investigator's medical school address on the front. Following data analysis, results were reported back to the students and discussed through small group meetings with the investigator and the teacher at each school.

Results

Demographic Characteristics. Table 1 presents the demographic characteristics of the sample from each school. While the two subgroups are approximately equivalent as to age, sex, and marital status, they are very different with respect to racial-ethnic status, religion, and social class.

TABLE 1.—*Demographic characteristics of the two study populations. Determination of social class was based on Hollingshead's Two Factor Index of Social Position.*[6]

	Middle-Class School	*Lower-Class School*
Total	180	154
Age		
Mean (years)	17.6	17.6
SD (years)	0.59	0.76
Sex		
Male	97	66
Female	83	88
Marital Status		
Never Married	178	144
Currently Married	2	5
Formerly Married	0	1
Unknown	0	4
Racial-Ethnic Group		
Black	1	20
Chicano	1	65
Oriental	1	5
White	172	51
Other	1	12
Unknown	4	1
Religion		
Jewish	1	2
Protestant	80	52
Roman Catholic	39	70
None	44	20
Other	7	2
Unknown	5	2
Social Class		
Head of Household—Occupation		
Professional—Managerial Worker, Major	41	3
Professional—Managerial Worker, Intermediate	28	5
Professional—Managerial Worker, Minor	40	6
Clerical, Sales, and Technical Workers	25	13
Skilled Manual Workers	27	46
Semi-Skilled Manual Workers	9	38
Unskilled Workers	1	22
Unknown	9	21
Head of Household—Education		
Post-Graduate Degree	30	1
College Graduate	45	12
One Year College+	40	10
Grade 12	38	25
Grades 10 through 12	11	23
Grades 7 through 9	10	36
To Grade 6	2	35
Unknown	4	12

Because of these school differences the presentation of the remaining data will be arranged according to school attended. Further, because of the potential effect of gender on sexual and contraceptive behavior, the data will also be presented according to the sex of the respondent. In order to simplify reading the tables and to facilitate comparison between rows, the remaining tables (with one exception—Table 14) are presented in terms of percentage.*

Sexual Norms. The respondents were asked under what conditions they approved of sexual intercourse for a man and a woman. Table 2 shows the percentage of each sub-group which approved, under five different conditions.

The respondents also were asked about their attitude toward unmarried men and women living together. The percentage of those approving is shown in the first line of Table 3.

Sexual Knowledge. The respondents were asked what were their most complete and factual sources of information on sexual matters. Their responses are shown in Table 4.

Sexual Opportunities and Deterrents. The respondents in the middle-class high school were asked about the extent to which opportunity or lack of opportunity influenced their sexual behavior (this question was added to the research instrument for this school at the suggestion of the

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*When no data were available from a given respondent(s) on a particular item of the questionnaire (a situation which occurred with low frequency), percentage figures were calculated by correspondingly decreasing the size of the sample. The N used for calculation is indicated in each table. The maximum size of the N for each of the four sub-groups of the sample is shown in the two rows under sex in Table 1.

TABLE 2.—*The percentage of respondents who agree with the acceptability of sexual intercourse under five different conditions for a man and for a woman. Data arranged by sex and social class.*

	Males		*Females*	
Acceptability of Sexual Intercourse	*Middle-Class School N=97*	*Lower-Class School N=66*	*Middle-Class School N=83*	*Lower-Class School N=88*
For a Man				
Only when married	12	8	11	17
When engaged*	79	73	67	51
When in love†	71	65	55	48
With good friend*	44	48	20	20
With acquaintance†	27	36	14	14
For a Woman				
Only when married†	16	26	25	42
When engaged*	83	71	66	50
When in love†	69	61	52	42
With good friend*	37	39	14	16
With acquaintance*	20	26	5	9

*Indicates that a chi square analysis of data is significantly different at <.001.

†Indicates that a chi square analysis of data is significantly different at <.01.

TABLE 3.—*The percentage of respondents who approve of unmarried cohabitation, contraception for minors without parental consent, and abortion, arranged by sex and social class.*

	Males		*Females*	
Respondent Approval	*Middle-Class School N=97*	*Lower-Class School N=66*	*Middle-Class School N=83*	*Lower-Class School N=88*
Unmarried cohabitation*	75	71	54	47
Contraception for minors without parental consent	75	79	69	67
Abortion*	67	35	64	30

*Indicates that a chi square analysis of data is significantly different at <.001.

TABLE 4.—*The percentage of respondents who report parents, friends, school, books and magazines, television and movies, and other sources as their most complete source of sexual information, arranged according to sex and social class.*

	Males		*Females*	
Sources of Sexual Information	*Middle-Class School N=97*	*Lower-Class School N=66*	*Middle-Class School N=83*	*Lower-Class School N=88*
Parents	11	11	12	13
Friends*	32	59	28	50
School*	42	8	45	16
Books and Magazines†	19	12	24	30
TV and Movies	3	12	7	9
Other	9	20	11	8

*Indicates that a chi square analysis of data is significantly different at <.001.

†Indicates that a chi square analysis of data is significantly different at <.05.

TABLE 5.—*The percentage of respondents from the middle-class school who reported that lack of opportunity had been a factor on some occasion in their not having sexual intercourse.*

	Middle-Class Male N=97	*Middle-Class Female N=83*
No opportunity	17	12

TABLE 6.—*The percentage of respondents who indicated various deterrents which have prevented them from having sexual intercourse on some occasion, arranged according to sex and social class.*

	Males		*Females*	
Deterrents to Sexual Intercourse	*Middle-Class School N=97*	*Lower-Class School N=66*	*Middle-Class School N=77*	*Lower-Class School N=88*
Felt it was wrong*	13	29	31	56
Feared pregnancy*	36	35	70	42
Feared social disapproval	6	9	17	15
Did not like person†	23	17	36	11
Feared disease	18	20	12	14

*Indicates that a chi square analysis of data is significantly different at <.001.

†Indicates that a chi square analysis of data is significantly different at <.01.

TABLE 7.—*The percentage of respondents who have been sexually active and, of these, the percentage who become pregnant or are aware of causing a pregnancy, arranged according to sex and social class. (N shown as: Total N/Sexually Active N).*

	Males		*Females*	
	Middle-Class School N= 97/52	*Lower-Class School N= 66/42*	*Middle-Class School N= 83/48*	*Lower-Class School N= 88/42*
Respondents having sexual intercourse	53	64	58	48
Respondents having sexual intercourse who became involved in at least one pregnancy*	2	20†	12.5‡	20

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*Indicates that a chi square analysis of data is significantly different at <.05.

†One man reported two pregnancies.

‡Two women reported two pregnancies.

TABLE 8.—*The percentage of sexually active respondents who reported having sexual intercourse once, a few times, several times per month, every week, several times per week, arranged according to sex and social class.*

	Males		*Females*	
Frequency of Sexual Intercourse	*Middle-Class School N=52*	*Lower-Class School N=42*	*Middle-Class School N=48*	*Lower-Class School N=40*
Once	8	12	8	18
Few times	46	31	40	40
Several/month	29	36	23	20
Every week	8	21	15	15
Several/week	10	0	15	8

TABLE 9.—*The percentage of sexually active respondents who have had one, two, three or four, five to ten, or more than ten sexual partners, arranged according to sex and social class.*

	Males		*Females*	
Number of Partners	*Middle-Class School N=51*	*Lower-Class School N=39*	*Middle-Class School N=48*	*Lower-Class School N=42*
1	49	49	60	62
2	16	13	13	19
3-4	24	26	19	12
5-10	2	5	4	5
>10	10	8	4	2

TABLE 10.—*The percentage of sexually active respondents who enjoy sexual intercourse a great deal, moderately, little, and not at all, arranged according to sex and social class.*

	Males		*Females*	
Enjoyment of Sexual Intercourse	*Middle-Class School N=51*	*Lower-Class School N=42*	*Middle-Class School N=47*	*Lower-Class School N=38*
Great deal*	82	81	64	53
Moderately	14	14	28	29
Little	4	0	4	8
Not at all	0	5	4	11

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*Indicates that a chi square analysis of data is significantly different at <.01.

school principal). The results are presented in Table 5. The respondents were also asked about five psychological factors which might deter them from having sexual intercourse. Table 6 shows the percentage of each sub-group which reported that one of the five factors was a deterrent on some occasion.

Sexual Behavior. The respondents were asked about their actual sexual behavior. Data on the percentage having sexual intercourse and, for this sexually active sub-group, the frequency of intercourse, the number of partners, and the degree of enjoyment of intercourse are presented in Tables 7, 8, 9, and 10.

The mean age and standard deviation of first sexual intercourse was 16.2±1.4 and 15.8±1.7 for the middle-class and lower-class schools respectively.

Contraceptive Norms. The respondents were asked about their preferences regarding the currently available contraceptive methods. Their responses are recorded in Table 11. They were also asked about their attitude toward the availability of contraception without parental consent. Data regarding this are shown in line 2 of Table 3.

Contraceptive Knowledge. The respondents were asked when the fertile period occurred during the ovulatory cycle. The results are shown in Table 12, where the data are further broken down for females according to the extent of their sexual behavior.

Contraceptive Behavior. The sexually active respondents were asked about actual contraceptive behavior. Differences between sub-groups were relatively minor and therefore the data are not presented in tabular form. The methods used most commonly (that is, by 40 to 60 percent of the

TABLE 11.—*The percentage of respondents who would prefer oral contraception, IUD, condom, rhythm, and all other methods of contraception for themselves, arranged according to sex and social class.*

	Males		*Females*	
Preferred Contraception	*Middle-Class School N=89*	*Lower-Class School N=47*	*Middle-Class School N=79*	*Lower-Class School N=64*
Oral contraception*	65	26	65	58
IUD*	1	6	23	13
Condom*	17	19	1	0
Rhythm†	7	19	3	14
Nothing	9	13	3	11
Other*	0	17	5	4

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*Indicates that a chi square analysis of data is significantly different at <.001.

†Indicates that a chi square analysis of data is significantly different at <.05.

respondents) in the past were withdrawal, rhythm and condom. About 25 percent of the respondents reported having used oral contraception, and about 40 percent reported using nothing at all on some occasions.

Abortion Norms. The respondents were asked about their attitude toward abortion. The percentage of those approving is presented in the last line of Table 3.

Procreative Norms. All respondents were asked how many children they desired to have. These data are presented in Table 13.

Procreational Outcomes. The sexually active respondents were asked whether they had ever become pregnant or caused a pregnancy. For those involved in a pregnancy, the outcome of that pregnancy was determined. These data are shown in Tables 7 and 14.

Discussion

The results of this survey provide information about how a sample of California suburban high-school students think, feel and behave with respect to sexuality, contraception and procreation. They also characterized the differences which exist within the sample when it is subdivided according to sex and social class. In this section I will discuss these two areas together and then describe a simple model which I believe will be helpful to physicians in integrating the various aspects of this subject area.

The great majority of this sample approve of pre-marital intercourse for both men and women (Table 2). However, this approval becomes weaker as the situation in which intercourse occurs moves from a highly-committed, love relationship to a casual one. Approval also becomes weaker when it is the behavior of women rather than men which is being considered. Analysis within the sample reveals that female respondents, especially lower-class females, are more likely not to approve of pre-marital intercourse than are the men. These results are similar in their basic form to those reported by Reiss from other parts of the country.[7,8] In general they suggest the existence of a peer-group atmosphere which is relatively supportive of pre-marital sexual intercourse between two adolescents who have a loving relationship. Further evidence for a supportive atmosphere comes from the data in this study which show that a clear majority of respondents approve of unmarried cohabitation and the provision of contraception to teenagers without parental consent (Table 3). Interestingly, while there are no significant sub-group differences with respect to the provision of contraception, female respondents are significantly less likely to approve of unmarried cohabitation. This probably reflects, among other things, the traditional reluctance of women to proceed too far in an intimate relationship out-

TABLE 12.—*The percentage of respondents who correctly answered when the fertile period occurred during the menstrual cycle, arranged according to sex and social class and, for females, according to whether or not they have had sexual intercourse.*

	Males		*Females*	
	Middle-Class School N=97	*Lower-Class School N=66*	*Middle-Class School N=83*	*Lower-Class School N=88*
Knowledge of fertile period*	38	29	63	34
Sexually active	..	..	77	36
Not sexually active	..	..	43	33

Middle-Class Sexually Active/Non-sexually Active Females N=48/35.

Lower-Class Sexually Active/Non-sexually Active Females N=42/46.

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*Indicates that a chi square analysis of data is significantly different at <.001.

TABLE 13.—*The percentage of respondents who indicated a desire for zero through six or more children, arranged according to sex and social class*

	Males		*Females*	
Number of Children Desired	*Middle-Class School N=88*	*Lower-Class School N=66*	*Middle-Class School N=83*	*Lower-Class School N=86*
0	11	15	5	12
1	5	6	10	2
2*	64	47	58	45
3	15	11	18	12
4†	1	11	7	17
5	2	5	1	3
6*	2	6	1	8
Mean number of children desired	2.06	2.33	2.23	2.64

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*Indicates that a chi square analysis of data is significantly different at <.05.

†Indicates that a chi square analysis of data is significantly different at <.01.

TABLE 14.—*Frequency of pregnancy outcomes, arranged according to sex and social class.*

	Males		*Females*	
Pregnancy Outcomes	*Middle-Class School*	*Lower-Class School*	*Middle-Class School*	*Lower-Class School*
Already married	0	0	0	0
Got married	0	3	0	0
Gave baby for adoption	0	0	1	0
Kept baby, unmarried	0	1	0	4
Legal abortion	1	0	5	3
Illegal abortion	0	2	0	0
Miscarriage	0	3	2	1
Total number of pregnancies	1	9	8	8

side of some formal social institution such as marriage.

An examination of the respondent's sources of sexual information indicate that few report their parents as important sources (Table 4). Friends, school, and books and magazines are the most frequently endorsed sources, in that order. Friends are more important for the lower-class adolescents, school for the middle-class group. This finding may be quite significant in that, in this particular sample, the lower-class school had no sex education program while the middle-class school had a comprehensive program, one which was well received and popular among the students.

When this investigation was initiated there were some at the middle-class school who believed that lack of opportunity was an important reason that adolescents do not become sexually active. A question on this issue was added to the questionnaire. The results (Table 5) indicate that only a few students report being deterred from sexual activity by lack of opportunity, and even in those few it was only "on some occasions."

Five psychological deterrents to intercourse were important for the respondents (Table 6) and in three there was considerable sub-group variation. Lower-class women were more likely than others to report being deterred because they felt that sexual intercourse was wrong. Middle-class women were more likely than other sub-groups to be deterred by fear of pregnancy and by not liking the other person. Over all, the most important deterrent was the fear of pregnancy, strengthening the view that practical considerations were more important than moral considerations in this sample's sexual behavior.

All these positive and negative factors—the opportunities, the deterrents, the social norms—combine with various sexual and non-sexual motives to produce some level of sexual activity in each respondent. In this sample, the majority of respondents have had sexual intercourse (Table 7). However, the level of activity was relatively low or new, or both, because about half of those already sexually active report having intercourse only "once" or "a few times" (Table 8) and about the same proportion reported having only one partner (Table 9). These findings are quite similar to those in a comparable national sample.[3]

Within sample, analysis revealed that there were no sex or social class differences with respect to how many respondents were sexually active, the frequency of intercourse, or the number of sexual partners. When this is considered together with the significant sub-sample differences in attitude toward pre-marital intercourse, it appears that women, especially those in the lower-class, are more likely to be sexually active while disapproving of it, and thus have conflict about their sexual activity. Such a conflict may play a part in the fact that while sexual activity was generally a source of considerable enjoyment for the whole sample, there was some tendency for the women respondents to report moderate as opposed to a great enjoyment (Table 10). Whether this apparent conflict also leads to ineffective contraception and unplanned conceptions cannot be decided from so small a sample. However, such an hypothesis finds support in other reports[9,10] and is consistent with the remainder of the findings, discussed below.

Most of the sexually active respondents had used either no contraception or a poor method (such as withdrawal or rhythm) on some occasion in the past. This corresponds well with current national findings.[3] On the other hand, the data on preferred contraception show that oral contraception was the most desired method. They also show considerable within-sample differences, with the intra-uterine device (IUD) favored by women, the condom by men and rhythm by the lower-class sub-samples. (This latter finding may well be the result of the religious differences which coincide with the social class differences in this sample. See Table 1). Lower-class males seem to have special contraceptive preferences with less orientation toward oral contraception and more toward other, less effective methods (mostly withdrawal and foam).

Only about one-third of the respondents knew correctly when the fertile period occurred during the menstrual cycle, with the exception of the middle-class women (Table 12). Within this sub-group, it actually was only the sexually active who were significantly more informed, three-fourths of them being correct in their estimation of the fertile period. This perhaps reflects the result of some interaction between the sex education program in the middle-class school and the needs created in the female respondents by their own sexual activity. It is interesting to note that the data in Table 12 parallel closely the data on fear of pregnancy seen in line 2 of Table 6, suggesting that among the sexually active, this fear provides one of the motivational links between exposure to sexual and contraception information and the acquisition of knowledge.

The entire group of respondents desired an average of 2.3 children (Table 13), with middle-class men having the lowest mean and lower-class women the highest. There was some tendency for more of the middle-class respondents to desire two children and for more of the lower-class respondents to desire four.

Among the respondents who are sexually active, unplanned pregnancy occurred with a frequency as high as 20 percent in two of the sub-samples (Table 7). Although the middle-class men reported significantly fewer pregnancies, it is quite likely that this difference results from their not being informed by the girl when a pregnancy has occurred. This conclusion is supported by the data on pregnancy outcomes in Table 14 which show that virtually all the pregnancies in the middle-class women had an outcome which could be concealed from the male. In contrast, a number of lower-class pregnancies went to term.

With respect to abortion, approval is significantly divided along social class lines, with the lower-class groups showing much less approval (again, this finding may be based primarily on religious differences).

While the numbers in Table 14 are far too small to extrapolate safely to a larger population, the fact that three pregnancies reported by lower-class men led to marriage does suggest that there may have been a number of lower-class women who married as a result of a pregnancy and dropped out of high school (and, thus, out of this sample). This possibility together with the lower pregnancy rate reported by middle-class men and the significant sub-sample differences in abortion norms support the general conclusion that ways of coping with unplanned pregnancy vary considerably by sex and social class and that the pregnancy rates in this sample—certainly for the middle-class men and quite possibly for the lower-class respondents in general—represent low estimates.

A useful model for integrating this subject area is depicted in Chart 1. The basic concept is that of the probablistic relationship between sexual intercourse and pregnancy, a relationship which can be considerably influenced by contraceptive behaviors. The chart depicts how these three sets of behaviors—namely heterosexual, contraceptive and pregnancy behavior—all inevitably linked by human physiology, are separately affected by a number of different social and psychological factors. In this paper, contemporary data regarding many of these factors have been presented. Where

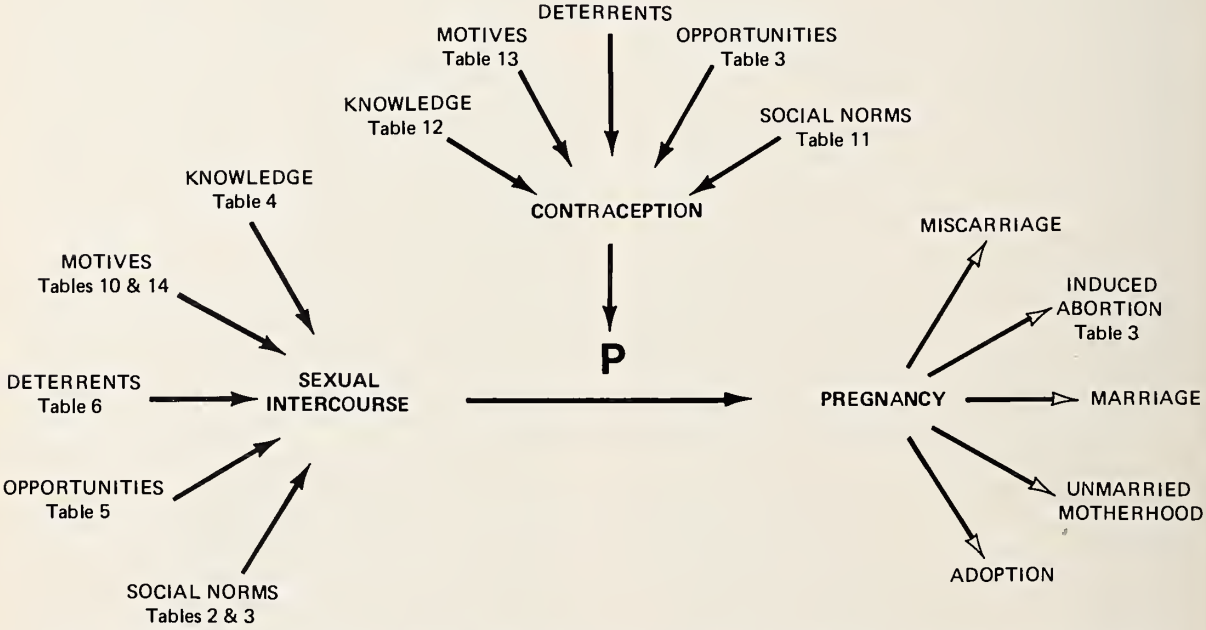

Chart 1.—A diagramatic model of the probabilistic relationship between sexual intercourse and pregnancy, indicating that the latter occurs following sexual intercourse with a certain probability, P. This probability is subject to considerable influence by contraception and contraceptive behavior. The model includes a variety of the psychological and social factors which influence sexual and contraceptive behavior. It also includes the alternate outcomes, largely behavioral, which may follow after a pregnancy.

applicable, this is indicated in the chart by listing the relevant table(s) under the appropriate psychological or social factor.

Each of these three major fields of behavior must be considered by the physician in dealing with the related problems presented to him by his patients. Thus, in a discussion of sexuality, the physician cannot separate out and omit a consideration of the need for contraception or the possibility of pregnancy. In prescribing contraception he must similarly take into account the effect of his action on the patient's future sexual behavior and his or her whole orientation toward pregnancy and childbearing. And in helping the patient to deal with an imagined or real pregnancy he must be able to look back in the process and help the patient to consider the sexual and contraception steps which led up to it initially. For a further discussion of these subject areas, the physician may consult other more detailed sources.[11,12,13]

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Finger Tip Amputations

Repair of finger tip amputations depends upon the slope of transsection and how much of the tip has been amputated. Type 1 and 2 injuries are easily handled in the emergency room by local flaps with results acceptable by functional and economic criteria. Type 3 amputations with losses of less than 25 percent can be repaired by primary closure. Losses of 50 percent or over are best treated by local or "distant" flaps from the involved or adjacent fingers or palm. Each style of flap and technique has advantages and disadvantages.

Review of Procedures and Applications

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THE MANAGEMENT OF FINGERTIP AMPUTATIONS is characterized by as much confusion as there is variety of repair. A review of our experience has led to the recognition of certain functional and economic goals. Certain patterns of injury occur which are categorized into types of injuries. In dealing with each type of injury the method of repair is selected to satisfy the goals outlined.

Goals

Primary goals of repair of both major and minor amputations have been well outlined by Beasley and Brody.[1,2] (See Figure 1.) The single most important goal is that of a useful, functionally sensitive finger tip. Secondary goals, although important economically, must not detract from providing a useful tip.

There are three types of major finger tip amputations. (See Figure 2.)

Type 1—The guillotine type without bony exposure wherein the entire finger tip loss is perpendicular to the long axis of the finger.

Type 2—The forward slope wherein the dorsal margin is proximal to the volar. Bone exposure is usually at the nail bed and distal portion of the phalanx.

Type 3—The backward slope wherein the volar surface is proximal to the dorsal. Bony exposure is on the volar surface.

In the emergency room, care of finger tip amputations must be based on distinguishing between major and minor losses. The major finger tip amputation is characterized by a wide exposure of bone, tendon, and nerve. These injuries require closure by local or distant pedicle flaps. (See Figure 3.)

Minor finger tip amputations are characterized by injuries usually involving less than 25 percent of the distal phalanx. Occasionally the entire tip may be involved. However, for the injury to be considered as one of the minor category, soft tissue coverage must be present for protection of underlying structures. (See Figure 4.)

Operative Repair

Techniques for Minor Repair

Minor amputations of tissue comprising less than 25 percent of the tip (see Figure 5) do not require surgical repair. These injuries are treated by initial cleansing with debridement of nonviable tissue and the application of a non-adherent

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dressing. The wound is kept clean by soaking the injured finger in lukewarm, soapy water three times a day followed by gentle cleansing with a gauze sponge or clean washcloth. Following these soaks, the wound is air-dried and re-dressed. The regimen is continued until spontaneous closure occurs. This phenomenon results from peripheral ingrowth of epithelium from surrounding uninjured wound margins, as well as wound contracture.

Amputations of tissue comprising more than 25 percent of the tip are considered minor if sufficient soft tissue remains to cover and protect underlying bone, tendon and neurovascular structures. These are treated by initial debridement of non-viable tissue and immediate split-thickness skin grafts. Grafts are obtained from non-hair-bearing areas—for example, lateral high thigh, buttock region, or anterior forearm. They are cut between thin and medium thickness, 0.010 to 0.012 inches. These grafts are sutured in place with non-absorbable stitches left long and tied over a stent dressing. Occasionally in older wounds with existing healthy granulation tissue, the grafts are simply taped in place with steristrips. Dressings of moistened cotton are then used over a non-adherent gauze to immobilize the wound area. Grafts are inspected in five days and sutures are removed in seven to ten days. (See Figures 6 and 7.)

Techniques for Major Amputation

The methods of repair of Type 1 and 2 finger tip amputations are straightforward and easily performed with local, adjacent flaps.

Type 1. Guillotine amputations are the most frequently encountered injuries. These are usually secondary to a door-slamming crush injury. (See Figure 8.) They are easily handled by local flaps as described by Kutler and Fisher.[4,7] (See Figures 9 and 10.) These are triangular flaps raised bilaterally and advanced distally and toward the midline of the finger. They are based on and nourished by their intact subcutaneous attachment. Incisions are extended far enough into the subjacent soft tissue to allow mobilization of the triangles. Donor defects are easily closed in a straight line. (See Figure 11.)

If the bone is exposed and length is to be preserved, this injury is considered in Type 3 repairs. If length can be sacrificed, as in the loss of the ring finger or little finger in elderly patients (see Figure 3), the exposed bone is resected to a level 3 to 5 mm deep to the surface before elevating Kutler flaps.

Type 2. Forward sloping amputations, (see Figure 12), are repaired by mobilization of volar skin dorsally. Occasionally a complementary excision of subcutaneous tissue is necessary to allow mobility of the flaps. (See Figure 13 A and C.) The volar flap is sutured to the remaining soft tissue or nail. Often a single midline triangle of tissue is mobilized dorsally allowing the lateral flaps to close medially and proximally. (See Figure 13 B and D.) This obviates unsightly, lateral dog-ears. Midline volar scars are neither cosmetically nor functionally bothersome to the patient. (See Figures 14 and 15.)

In both of these repairs the finger tips meet the primary goals. Secondary goals are also satisfied, as the procedures can be performed in the emergency room on adults and cooperative youngsters, and require no separate donor site.

Type 3. Reflecting the uncertainty and difficulty in its management, this type of amputation is characterized by a wide variety of repairs. First, a word on completely amputated tips usually brought in by an expectant, well-meaning parent or friend.

Amputated tips are not replaced. (See Figure 16.) These tips are usually crushed, dirty and non-viable. In light of the added expenditure of the patient's time and resources, this surgical exercise cannot be justified. The replaced tip soon becomes necrotic and, at best, only a few millimeters of poorly viable skin are gained. (See Figure 17.) The only exception is in a child, less than three years of age with an available, cleanly transected, non-crushed tip. If the amputation comprised less than 50 percent of the distal tip, this can be replaced, with expectation of excellent results.

Part of the difficulty in repair of Type 3 finger tip amputations stems from unclear designations in the literature as to the exact defect to be covered. As a basis for discussion of the various types of repairs, we will regard the distal tip as divided into quartiles transversely disposed. (See Figure 18.)

25 Percent Losses. Volar flaps are easily raised for coverage of the smaller amputations with a good bit of soft tissue. Exact approximation is unnecessary. A small amount of separation, 4 or 5 mm, is acceptable, as detailed in the section under minor repairs. Larger amputations, approaching 50 percent vertically or diagonally disposed, are more easily handled with flap coverage.

FINGER-TIP REPAIR: GOALS

A. PRIMARY

1) FUNCTIONALLY SENSITIVE
2) DURABLE
3) COSMETICALLY SATISFACTORY
4) PAINLESS

B. SECONDARY

1) MINIMAL HOSPITAL STAY
2) MINIMAL WORK LOSS
3) PAINLESS DONOR SITE

Figure 1.—Details the primary and secondary goals of finger tip repair.

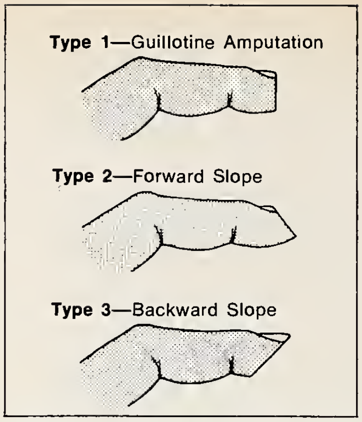


Figure 2.—Diagram showing the three types of finger amputations most commonly seen in the emergency room.

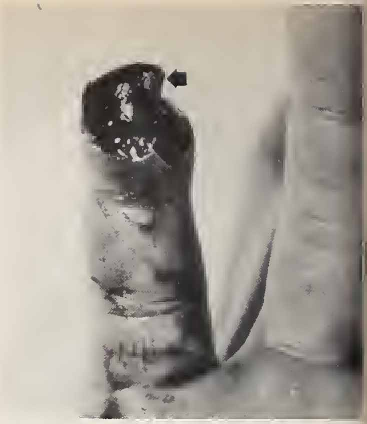


Figure 3.—Transverse finger tip amputatic in an elderly man. Note the exposure bone (arrow), the extensor and flex tendons are intact. Because of the patient age and the fact that this was the litt finger, the treatment of choice is resectic of bone and closure with local flaps.

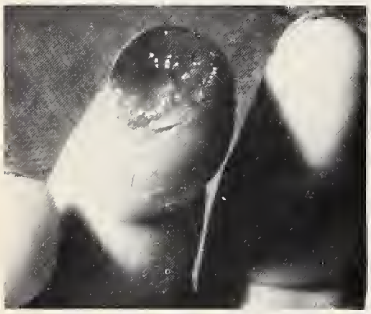


Figure 4.—An oblique finger tip amputation wherein there is an excellent subcutaneous bed without bony tendon or nerve exposure. This is a minor amputation and is to be treated with a skin graft.

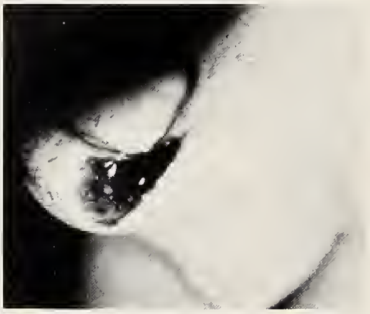


Figure 5.—An oblique finger tip amputation with sloping edges distally. Less than 25 percent of the tip involved. This is to be treated by local care and allowed to spontaneously epithelize from the circumferential margins.

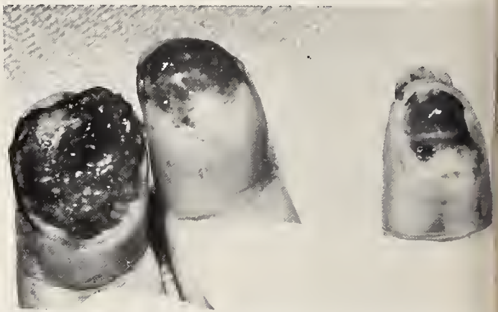


Figure 6.—Minor finger tip amputation with protective s tissue base. Treatment by cleansing, debridement of no viable tissue and closure with skin graft.

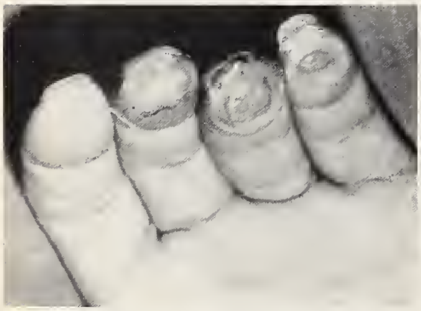


Figure 7.—Minor finger tip amputations seen in Figure 6, following early healing of skin grafts.

FIGURES 8 to 11
Illustrate Repairs of
Type 1
Guillotine Amputation

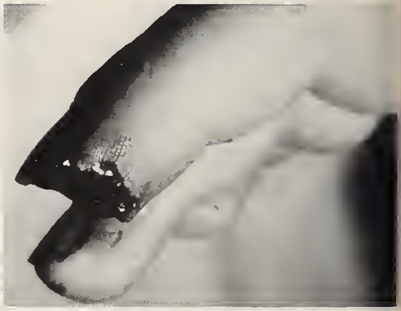


Figure 8.—Guillotine amputation, the kind mc frequently seen in the emergency room.

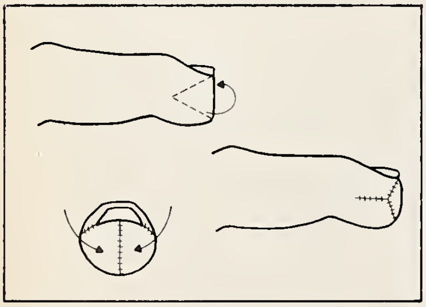


Figure 9.—The closure of the guillotine amputation with local triangular flaps advanced distally and toward the midline of the finger.

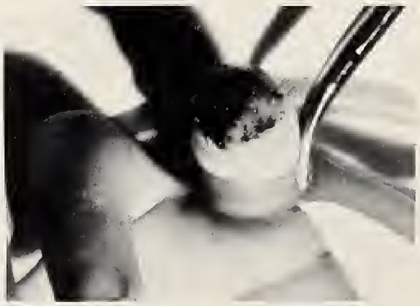


Figure 10.—Mobilized Kutler triangular flaps completing the closure of a Type 1 finger tip amputation.

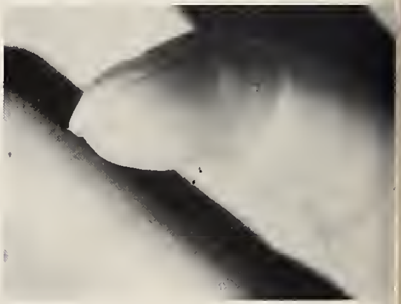


Figure 11.—The same finger shown in Figure three months after operation.

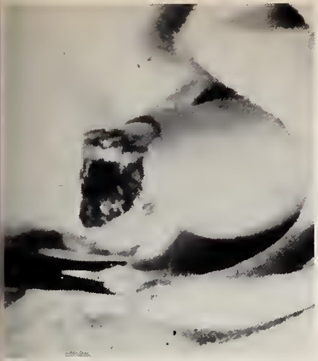


Figure 12.—Type 2, forward slope amputation.

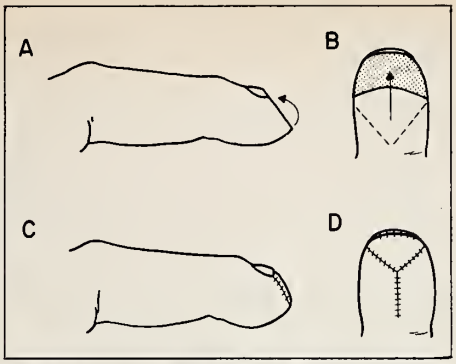


Figure 13.—Two methods of closure of Type 2 amputation. A and C demonstrate closure by simply bringing the volar skin to the nail bed or nail. B and D demonstrate mobilization of a single, volar triangular flap distally and superiorly with a linear closure of the defect.

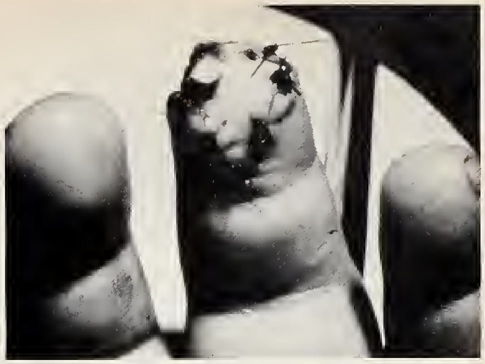


Figure 14.—The volar triangular flap closure of repair in Figure 12.

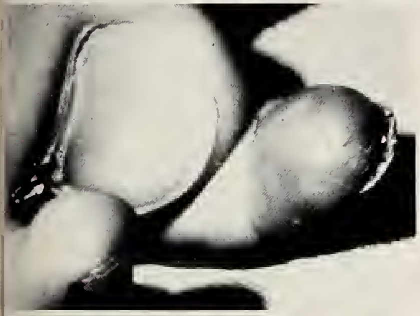


Figure 15.—Result three months after operation a midline volar triangular flap closure shown in Figure 12.

FIGURES 12 to 18 Illustrate Repairs of Type 3 Amputations

FIGURES 19 to 21 Illustrate Hueston's Local Rotational Flap

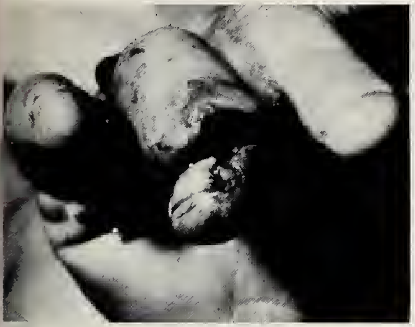


Figure 16.—Finger tip amputation in a four-year old child with the tip held on by a few subcutaneous fibers. Blood supply was not intact. The injury resulted from a door slam.

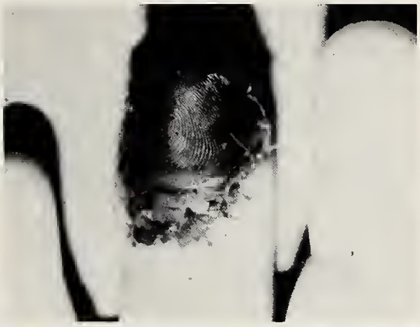


Figure 17.—Necrotic nonviable tip resulting from an injudicious attempt to replace the crushed finger tip seen in Figure 16.

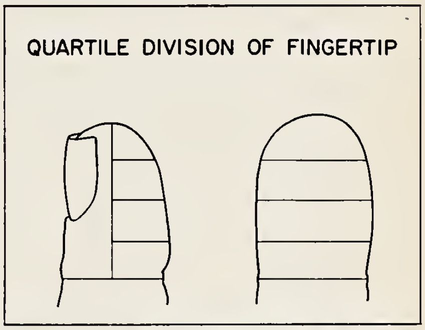


Figure 18.—The quartile division of finger tip.

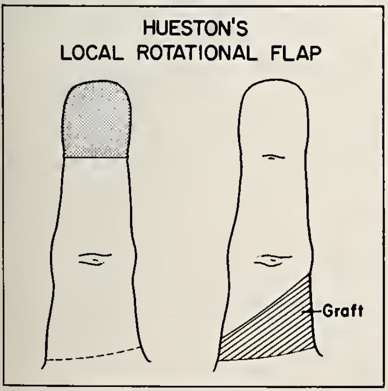


Figure 19.—Hueston's local rotational flap. This flap is based on a unilateral neurovascular bundle and rotated distally to cover finger tip amputations. The donor site left exposed is covered with a full or split-thickness skin graft.

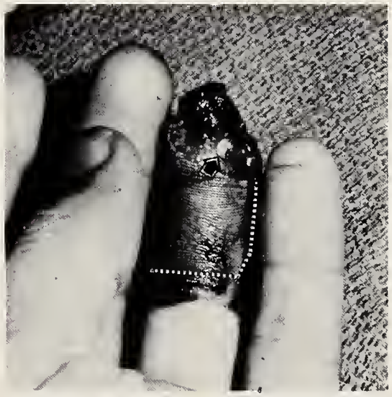


Figure 20.—Type 3 finger tip amputation on the ring finger of a workman desiring early return to work. Plan—shorten bone and cover exposed tendon (arrow) by Hueston's rotational flap. (See dotted line.)

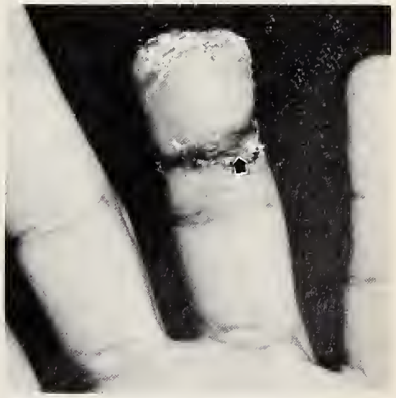


Figure 21.—Postoperative picture of the finger tip amputation depicted in Figure 20. Skin graft (arrow) well healed.

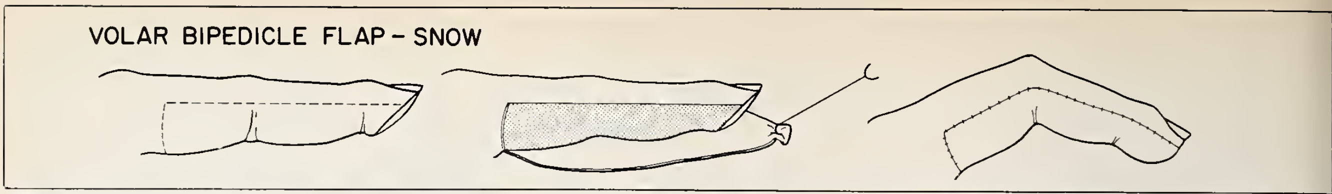


Figure 22.—Volar bipedicle flap of Snow, using the entire volar skin of the involved digit to be dissected and advanced distally to cover finger tip amputations. Resultant finger requires flexion at the intermediate and distal phalangeal joints with long linear scars resulting bilaterally.

FIGURE 22 (above) Illustrates Volar Bipedicle Flap-Snow
FIGURES 23 to 25 (below) Illustrate Unipedicle Dorsal Flap-Brucker

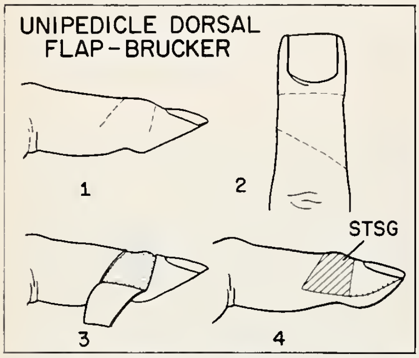


Figure 23.—Brucker's unipedicle dorsal flap raised at the dorsal aspect of the involved digit —1 and 2; the length of the flap extending the entire width of the digit, 3; elevated and advanced distally, 4. The donor site is covered with a split-thickness or full thickness skin graft.

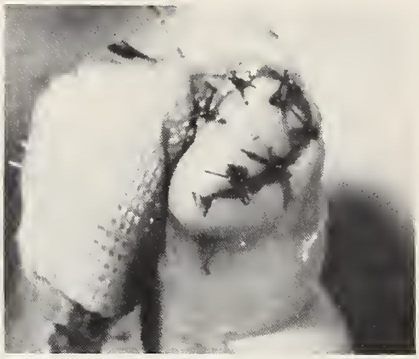


Figure 24.—The unipedicle flap of Brucker advanced distally and sutured in place. Note the dog-ear which occurs with this advancement. This is not corrected at the time of the operation, as impairment of the pedicle would result. The dog-ear softens in time and is not objectionable cosmetically.

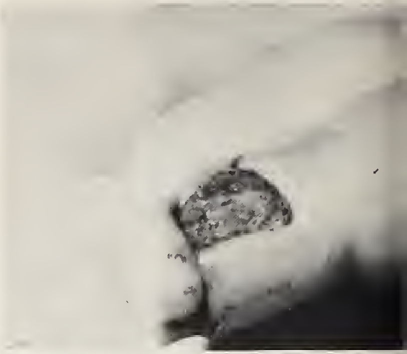


Figure 25.—The dorsal surface of the finge after the unipedicle flap has been elevated. Thi is easily covered with a skin graft.

50 Percent Losses. These require dorsal or distant flaps. "Distant" flaps are defined as cross-finger or palmar flaps. Local flaps are from the involved finger, whether dorsal or volar in origin. It has been shown that these flaps give excellent results, both cosmetically and functionally.[6,11] With the adequacy of local tissue and the variety of procedures to be detailed below, it seems reasonable to dispense with the distant flaps from the chest and abdominal walls for the single finger tip amputations. The latter provide bulky, cosmetically inferior and poorly sensitive tips.

Varieties of Finger Flaps

Hueston's Local Rotational Flaps. This volar flap based on a single neurovascular pedicle is rotated distally for finger tip resurfacing. (See Figure 19.) It is described as useful for all finger tip amputations, but probably should be reserved for those of Category 3—50 to 100 percent. The greatest distance of rotation is calculated in the placement of the dorsal midlateral incision and continued proximally to cross the second crease proximal to the injury thus usually denervating the ipsilateral half, as described by Hueston.[6] (See Figure 20.) The flap is mobilized and rotated forward. The proximal defect is then covered with a full thickness skin graft. (See Figure 21.)

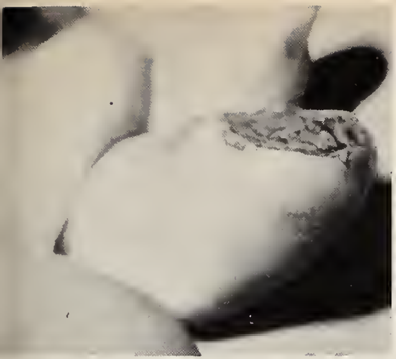
Volar Bipedicle Flap. A bipedicle volar flap, described by Snow and Bunnel (see Figure 22) allows for finger tip resurfacing by elevating the entire volar surface of the involved finger with the neurovascular bundles intact. The flap is advanced forward to cover the defect. Additional length is easily obtained by flexing the interphalangeal and distal interphalangeal joints.[10]

Snow reports no flexion contracture in defects involving the entire distal phalanx.

Unipedicle Dorsal Flaps. Brucker advocates a local flap technique for finger tip amputations.[3] A unipedicle dorsal flap is raised on the injured finger, based on the ipsilateral neurovascular bundle and rotated volarward and distally for coverage. (See Figures 23 and 24.) The dorsal donor site is covered with a split thickness skin graft. (See Figure 25.)

Brucker's flap is best reserved for oblique finger tip amputations of the 25 to 50 percent category. The major skin loss to be covered by this flap should be more to the side upon which the flap is based.

Cross-Finger Flap. Gurdin popularized this



gure 26.—A typical Type 3 finger tip amputa-
n. This is the result of the finger tip injury in
e patient shown in Figures 16 and 17 after
bridement of the nonviable portion.

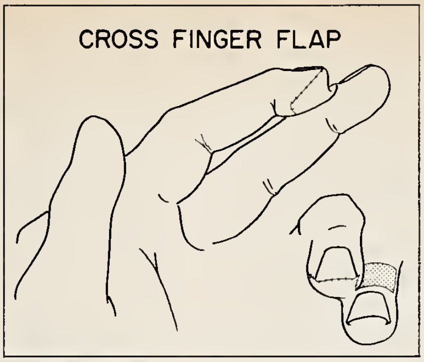


Figure 27.—Diagrammatic demonstration of the cross-finger flap.

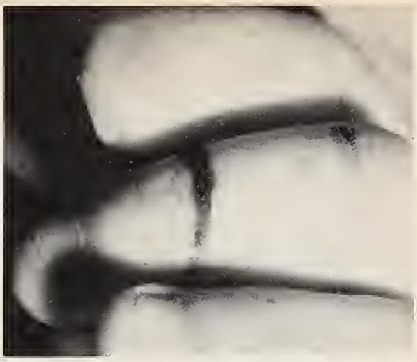
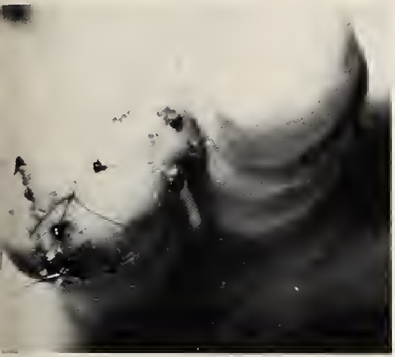


Figure 28.—The outlining of a cross-finger flap, using the dorsal surface of the adjacent digit.



ure 29.—The "end-on" view of the cross-
ger flap sutured in place.

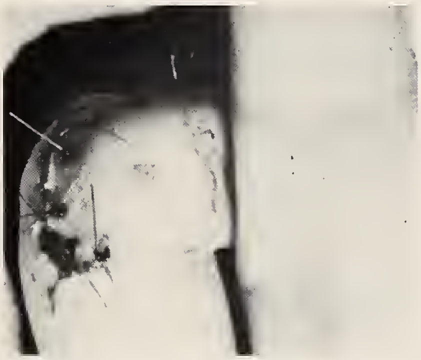


Figure 30.—View from the volar surface with the cross-finger flap in place. Both this view and Figure 29 were taken two weeks after operation and in preparation for division of the flap. Note sutures are left in place until after division of of the flap.

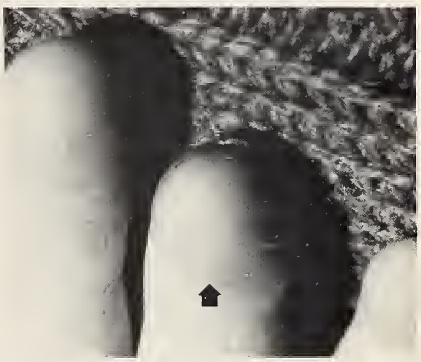
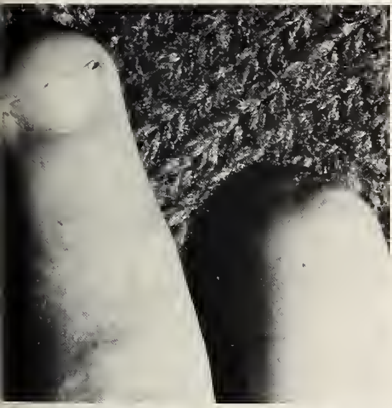


Figure 31.—The finger tip resurfaced with a cross-finger flap. This picture is three months after operation and is the same patient as in Figure 26.



ure 32.—The donor site on the dorsal aspect
the long finger. Note the absence of the nail
the amputated ring finger.

FIGURES 26 to 32
Illustrate the
Cross Finger
Flap

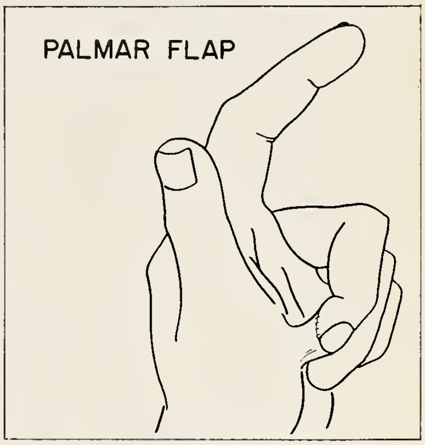


Figure 33.—The palmar flap.

"distant" flap. It consists of the elevation of a dorsally based flap from an adjacent finger to cover a finger tip amputation.[6] (See Figures 26, 27 and 28.) The flap is sutured in place (see Figures 29 and 30) and after 14 to 21 days, when mature and the crossed blood supply has developed, it is divided. The recipient finger may be fixed to the donor digit with a Kirschner wire or, preferably, simply immobilized in a bulky dressing. The donor site is covered at the initial operation with a medium split-thickness skin graft, 0.015 inches. The donor site and the amputated finger are then cosmetically acceptable.[4] (See Figures 31 and 32.)

The cross-finger flap has been the most versatile method of resurfacing Type 3 finger tip amputations. There are several drawbacks to be discussed below as regards delayed reinnervation, staged procedures and possible contractures. Despite this the ease of procurement and satisfactory tips resulting make it the most popular flap used in this series.

Palmar Flaps. A "distant" flap is elevated on the palm, usually proximally based to cover the approximated finger tip amputation. (See Figure 33.) The donor site is covered with a split-thickness skin graft. Although the palmar flap has applicability for most major finger tip amputations, certain drawbacks (to be discussed) limit its usefulness.

Discussion of Kinds of Flaps

Innervation. Only Snow's bipedicle flap brings a completely intact, innervated flap to the finger tip. Others rely on reinnervation. That this is only a minor disadvantage has been shown by the excellent reinnervation studies detailed by Sturman and Duran.[11] With this study, they endorse and recommend cross-finger or palmar flaps for coverage of most finger tip amputations.

Operative Procedures. Both the cross-finger and palmar flaps require two procedures, the second stage being for detachment. The rest require only one procedure.

Flexion Contractions. The cross-finger flap, the palmar flap, and possibly Snow's bipedicle volar flap, could lead to flexion contractures secondary to the necessary positioning of the amputated finger. The palmer flap would be more likely to lead to a stiff joint in patients more than 40 years of age than would Snow's or the cross-finger flap. The dorsal flap and volar rotational flap require no flexion for tip resurfacing, obviating the possibility of flexion contractures.

Other Postoperative Complications. Painful donor sites might be expected to occur in the grafts of the palmar and volar rotational flap of Hueston. Both Snow's and Hueston's flaps require major dissection of intact, specialized palmar skin to allow mobilization of part of the entire volar surface of the involved digit. This could conceivably lead to painful neuromata formation. Long linear scars result, which could lead to scar contractures.

Operative Techniques

As with all operations on the hand, a tourniquet to maintain a bloodless field is mandatory. Operative procedures for Type 1 and Type 2 finger tip amputations are performed under digital, axillary block or general anesthesia, depending upon the preferencc of the surgeon and the adequacy of the facility. For Type 3 amputations requiring flap procedures, general or axillary block anesthesia is preferred. Nylon sutures of 5-0 are used for older children and adults. These are left in for ten days before removal. In flaps divided at 14 days, the sutures are removed following divisions. Chromacized catgut 5-0 is used for younger children. This obviates the necessity of suture removal in an uncooperative child. The extent of the hand dressing is inversely proportional to the age and directly proportional to the curiosity of the patient and the number of digits damaged. Generally a non-adherent gauze is used to cover the flap, and fluffed gauze is placed between the fingers to prevent maceration. A bulky dressing with the hand in a position of function helps to immobilize the involved digit and required flaps.

Conclusion

Minor finger tip amputations are viewed as requiring surgical repair—skin graft—if 25 percent or more of the tip has been amputated. Smaller injuries are treated by dressings.

Major amputations with slope configuration of Types 1 and 2 are treated with local flaps, usually in the emergency room without full admittance to hospital.

Type 3 amputations are the most difficult to treat because of the sometimes frightening loss of tissue and the variable exposure of tendon, bone and neurovascular structures. In general the cross-finger flap has been the most versatile and frequently used flap for finger tip amputations. Its ease of dissection and elevation, and the absence of postoperative donor site pain more than overcome the drawback that it is done in two stages and reinnervation is slower.

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Refer to: Mascovich PR, Behrstock B, Minor D, et al: Attitudes of obstetric and gynecologic residents toward abortion. Calif Med 119:29-34, Aug 1973

Attitudes of Obstetric and Gynecologic Residents Toward Abortion

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BARRY BEHRSTOCK, BA
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ARTHUR COLMAN, MD
San Francisco

As a follow-up to Wolf's study of attitudes of obstetrical housestaff toward therapeutic abortion,[5] the attitudes of 48 obstetrical residents in the San Francisco Bay area were evaluated by questionnaire and structured interview. Specific issues studied were: (1) Willingness to perform therapeutic abortion, (2) impact of therapeutic abortion on Resident Training Program, (3) attitudes toward different operational procedures, and (4) preferred physician-patient relationship with therapeutic abortion patients. Findings suggest that although there is recognition and acceptance by most residents of the social need for therapeutic abortion, considerable ambivalence persists.

THE NUMBER OF ABORTIONS performed and the ease with which they are obtained have been steadily increasing since 1967 when the present California Therapeutic Abortion Act was approved. In many California hospitals the policy is essentially abortion-on-request.* In San Francisco alone last year, 7,973 therapeutic abortions were performed, making the ratio of abortions to live births 532:1,000.[1]

The effect of such liberalized practice on the feelings and attitudes of the women receiving the abortions and the professionals delivering the abortion services has been the subject of much interest in the popular literature, but of little systematic research.[2,3]

In 1966, a questionnaire sent by Sherwin and Overstreet to California members of the American Board of Obstetricians and Gynecologists showed that most members favored therapeutic abortion where there is risk of material impairment of maternal physical or mental health, and where there is rape or incest.[4] These same indications were incorporated into the California Therapeutic Abortion Act in 1967. In that study only 21 percent of the members favored therapeutic abortion for purely socio-economic reasons.

In a study of 1970 by Wolf et al, a questionnaire was sent to full-time, attending and housestaff members of the Johns Hopkins Hospital Department of Obstetrics and Gynecology.[5]

---

*A woman doesn't have to have physical or psychiatric indications in order to obtain abortion. She may obtain one for socio-economic reasons, for example.

From the University of California, San Francisco, School of Medicine.

At the time the article was written the first three authors were third year medical students, Class of 1974. Dr. Colman is Assistant Professor of Psychiatry in Residence. The study was done during August 1971.

Submitted, revised, March 28, 1973.

Reprint requests to: Paul R. Mascovich, 470 Corbett St., San Francisco, CA 94114.

Eighty-eight percent of the responding physicians showed a willingness to perform abortion on request on women in the first trimester of pregnancy. Also in Wolf's study, younger physicians—residents and those who had recently completed their residencies—showed more liberal attitudes than older physicians.

The present study was developed to study the feelings and attitudes of obstetrics and gynecology housestaff members in hospitals in San Francisco and Oakland, California. We chose obstetrics and gynecology house staff for this study in order to replicate and expand on Wolf's findings. As he suggests, they are a critical group, since (1) they already perform many abortions in their service role in hospital clinics, (2) their attitudes toward abortion services provide a valuable chance to evaluate the current effect, in this regard, of medical education both in medical school and residency training, and (3) their feelings and attitudes will contribute to the future feelings and attitudes of the coming generation of obstetricians and gynecologists in private practice.

Method

The Interview

In previous research in this field, mailed questionnaires were used to obtain data.[4,5] This approach has well known problems due to the differences in interpretation of questions and to low return rates and consequent sample basis. For this study a structured interview was devised, in which a questionnaire was filled in by the researcher during a personal interview with each housestaff member. This enabled the housestaff member to clear up any misunderstandings about questions in the questionnaire; and it gave the researcher a more complete picture of the subject's feelings and attitudes through anecdotal information during the course of the interview. All the housestaff members were interviewed by the same researcher.

The questionnaire

Part of our questionnaire repeated Wolf's questions concerning willingness to perform abortions and concerning housestaff education. Additional questions concerning operational procedures and the physician-patient relationship were included. The specific questions are contained in the body of the results.

The subjects

The following residency programs were studied: 1. University of California (20 residents), which staffs the University of California, Moffitt, Children's and San Francisco General Hospitals; 2. Mt. Zion Hospital (three residents); 3. Kaiser Hospital, San Francisco (nine residents); 4. Highland County Hospital (five residents); 5. Kaiser Hospital, Oakland (11 residents).

Two residents—one from University of California and one from Kaiser, Oakland—were on vacation and therefore were not included in the study.

Among the residents, there were three women and 45 men. The ages ranged from 25 to 42, with a mode of 30. There were 41 whites, two Egyptians, and one each of black, Oriental, and Latin American. Their years of graduation from medical school ranged from 1954 to 1971, with a mode of 1969. Thirty-seven were married, nine were unmarried, and two were divorced. They were raised in the following religions: 19 Protestant, 13 Jewish, ten Roman Catholic, two Coptic Orthodox; and four had no religion.

Results and Discussion

Willingness to perform therapeutic abortion (See Table 1)

Of the residents, 47 (98 percent) said they perform therapeutic abortions. At the time of the study three of these 47 had not yet been asked to perform a therapeutic abortion, although they expressed a willingness to do so if asked. When they were asked about the factors which influenced their decision to perform an abortion, most of the residents who perform abortions responded as follows: (1) that it was part of their training program, and (2) that women should have the right to decide the fate of their pregnancy. Many also said that considerations of the population problem, unwanted children, and other socio-economic problems influenced their decision. Of the residents who will do abortions, 39 (83 percent) were willing to give abortion on request.

None of the residents doing abortions expressed any significant difference in attitude about giving an abortion to a minor as compared with a woman over 21, or to an unmarried as compared with a married woman.

There was considerable ambivalence expressed about using amniocentesis as compared with a vacuum aspiration abortion (given under 12

TABLE 1.—*Willingness to Perform Therapeutic Abortion*

	Yes	*No*	*Give less readily*	*Do not know*
Do you perform therapeutic abortions?	47*(98%)	1 (2%)	0	0
If you were the only one responsible for the decision, would you perform abortion on request of the woman?†	39 (83%)	8 (17%)	0	0
Would you perform abortion on request of a minor?†	39 (83%)	8 (17%)	0	0
Would you perform abortion on request of an unmarried woman?†	39 (83%)	8 (17%)	0	0
Would you give an amniocentesis abortion on request?†	37 (79%)	1 (2%)	6 (13%)	3 (6%)
Would you give abortion on request to a woman who is a "repeater"?†	34 (72%)	3 (6%)	9 (19%)	1 (3%)
Do you think it could become too easy for a woman to obtain an abortion?	22 (46%)	26 (54%)	0	0

*At the time of the study three of these 47 residents had not yet been asked to perform abortions, although they expressed a willingness to do so when asked.

†These questions were asked only of the 47 residents who perform therapeutic abortions.

weeks of pregnancy). Most residents said they would rather do a vacuum aspiration abortion than an amniocentesis abortion; six (13 percent) would in practice do amniocentesis less readily; and one (2 percent) would not do amniocentesis. The major reason given for this ambivalence is the greater risk of complications with amniocentesis. Also, many residents expressed a distaste for doing an abortion when the fetus is reasonably well formed and begins looking more and more like a full-term baby.

There was also much ambivalence concerning abortions for "repeaters"—women who have already had at least one abortion. In this case, nine (19 percent) of the residents would give an abortion less readily, and three (6 percent) not at all. Most of these residents resented what they described as the lack of responsibility on the part of the woman to use some adequate form of contraception; and they were reluctant to reinforce this irresponsibility by continuing to give the woman abortions. The 34 (72 percent) who would give abortions to repeaters recognized that a repeater represents a breakdown at some stage of contraception information or practice. Their solution to the problem, however, was not to withhold the abortion, but to try to deal with it by determining why the problem is there and by strongly urging the use of contraception.

Twenty-two (46 percent) of the residents felt that it could become too easy for a woman to get an abortion. The major reason given by these residents was that abortion should not be used as a primary means of birth control, but should at most be used as a back-up procedure in case of failure of contraception methods. The 26 (54 percent) who did not feel that it could become too easy for a woman to get an abortion felt that, in general, the medical risk and emotional trauma inherent in an abortion would prevent its general abuse.

TABLE 2.—*Attitudes Toward Abortion in Residency Training*

	Number	*Percent*
Do you feel obligated by your department to perform abortions?		
Yes	17	35%
No	29	60
Do not know	2	5
Do you feel that abortions take up too much of your time?		
Yes	15	31
No	26	54
Do not know	7	15
Have you seen any change in the quality of your training with an increase in the number of abortions performed?		
No change	23	48
Increase	8	17
Decrease	5	10
Do not know	12	25

Residency training (See Table 2)

Seventeen (35 percent) of the residents felt obligated to their departments and fellow residents to do abortions. Most of this group felt that, although abortions were not "required," their not doing them would unfairly increase the work load for the other residents in their program. Fourteen residents (34 percent) felt that abortions take up too much of their time.

Twenty-three (48 percent) of the residents saw no change in the quality of their training with an increase in the number of abortions performed. Eight (17 percent) saw an increase in quality; five (10 percent) saw a decrease in quality; and 12 (25 percent) indicated a lack of sufficient experience to make such an evaluation. The residents who saw an increase in quality reasoned that they are receiving more training in this procedure, which is a necessary and valuable part of the specialty of obstetrics and gynecology. Four of the five who saw a decrease in quality thought that a large volume of abortions takes too much time away from other equally important, or more important parts of their training.

TABLE 3.—*Attitudes Toward Various Operational Procedures for Abortion*

	Number	*Percent*
Is it important that the therapeutic abortion be performed by an Obstetrics/Gynecologist specialist?		
Yes	8	17%
No, but it should be done by an MD	17	35
No, a general MD or trained technician is satisfactory	22	46
Do not know	1	2
Presently the legal limit for therapeutic abortion is 20 weeks. If it were up to the discretion of the physician, what limit would you set?		
Less than 20 weeks	8	17
20 weeks	30	62
More than 20 weeks	7	15
Do not know	3	6
Do you prefer to perform vacuum aspiration abortions on an inpatient or outpatient basis?*		
Inpatient	5	11
Outpatient	41	85
Do not know	1	2
Is an operating room necessary?		
Yes	10	22
No	37	77
Do not know	1	2
Can a vacuum aspiration be done safely in a private office?		
Yes	24	50
No	22	46
Do not know	2	4
Do you prefer local or general anesthesia?		
Local	19	40
General	22	47
Do not know	6	13
If a woman wants local anesthesia will you give it to her?		
Yes	44	92
No	2	4
Do not know	2	4

*Asked only of the 47 residents who perform therapeutic abortions.

Operational procedures (See Table 3)

Eight (17 percent) of the residents believed that it is necessary that the abortion be performed by a gynecologist, and 17 (35 percent) believed that a physician with some training in doing abortions is needed, although not necessarily a gynecologist. Twenty-two (46 percent) felt that a trained technician with the supervision of a gynecologist would be satisfactory, such as might be the situation in an abortion clinic, with several technicians performing routine abortions and a specialist available to handle any complications.

The present legal limit for abortion in California is 20 weeks after the last menstrual period. When asked what limit they would set if it were left to their own discretion, 30 (62 percent) of the residents said they would keep the limit at 20 weeks, eight (17 percent) would make it less than 20 weeks, and seven (15 percent) would make it greater than 20 weeks. Three (6 percent) did not know.

Forty-one (87 percent) of the residents preferred to do vacuum aspiration abortions on an outpatient basis. Five (11 percent) preferred inpatient basis, and one (2 percent) did not know. Those who preferred outpatient care felt that inpatient care is not needed in most cases and that with outpatient care, time, money and emotional trauma can be minimized. Those who preferred inpatient care said they are better able to watch for complications under those conditions.

One of the major costs of an abortion is the hospital fee, and a substantial portion of this is for the operating room or its equivalent. Thirty-seven (77 percent) of the residents felt that an operating room is not needed for a vacuum aspiration abortion. They felt that aseptic conditions and facilities to handle complications should be available, however.

Twenty-four (50 percent) of the residents felt that a vacuum aspiration abortion could be done safely in a private office. Twenty-two (46 percent) did not, and two (4 percent) did not know.

Nineteeen (40 percent) of the residents preferred to use local anesthesia. Twenty-two (47 percent) preferred general, and six (13 percent) had not formed a preference. Forty-four (92 percent) of the residents said they would give a local anesthesia to the woman if she specifically requested it, while two residents (4 percent) said they would not.

TABLE 4.—*Attitudes Toward Effect of Abortion on Physician-Patient Relationship*

	Number	Percent
Is it necessary that the gynecologist doing the abortion also do the pre- and post-abortion examinations?		
Yes	29	60%
No	19	40
Do you know how and why the woman became pregnant?		
Yes	22	46
No	25	54
What is your reaction to being called an "abortionist"?		
Negative	20	42
Positive	2	4
No reaction	27	54

Physician-patient relationship and personal attitudes (See Table 4)

A woman receiving an abortion normally has contact with a gynecologist during the pre-abortion examination, during the actual operation, and during the post-abortion examination two to six weeks after the operation. Twenty-nine (60 percent) of the residents thought that the physician who did the operation should also do the pre-abortion and post-abortion examinations; and 19 (40 percent) thought that this is not necessary. Many who thought that it is necessary also remarked that it is practically impossible to achieve that ideal in a clinic staffed by residents because of their rotation of duties.

Twenty-two (46 percent) of the residents said that they usually know how and why the women they are dealing with became pregnant (that is, the psycho-social circumstances around the pregnancies); 25 (54 percent) said they do not usually know this. This question may be an indication of whether the physician sees a counsellor function as relevant to his role.

When asked what their reactions were to being called an "abortionist," 20 (42 percent) of the residents responded negatively, two (4 percent) responded positively, and 27 (54 percent) said they had no positive or negative reaction.

Discussion

The obstetrics and gynecology residents in this study displayed a number of attitudes which reflect the changing status of abortion in the medical profession, as well as in society. Despite the changing laws, increased emphasis in medical education and public debate, moral-ethical issues still permeate the subject of abortion and affect those in the medical profession. Certain trends are apparent from this study.

The movement away from external regulation of therapeutic abortion to a more direct and personal decision making process has meant that physicians must deal more directly and personally with their own ambivalent feelings around abortion. It was noted that most of the residents see a social need to perform abortions; but many also feel resentful that so much of their training time is concerned with abortions, which they see of little educational value beyond acquiring technical proficiency. There were anecdotal remarks from many residents expressing boredom and distaste with doing abortions, and ambivalence concerning amniocentesis and abortion for "repeaters." This suggests that complaints directed toward the usurpation of training time may screen the more emotion-laden issues relating to sexuality and the ethics of fetal destruction most often discussed in "abortion politics." Conflictual attitudes probably underlie the obstetrics and gynecology residents' concern for the development of more humanizing procedures and facilities for the abortion patient, on the one hand, while withdrawing from personal relationships with these patients and emphasizing the use of non-physicians and non-obstetricians in both procedural and counselling roles. Despite their commitment of providing abortion services for their patients, the role and label of abortionist remains stigmatized.

In the study by Wolf et al it was found that housestaff physicians were more willing to perform abortions than were physicians who had already completed their residency training. Wolf correlated this distinction to the amount of time the physician spent in the hospital, where, according to his findings, changes in the practice of and attitudes toward abortion first occur.[5] A comparison of the results of the present study to those of a study by Behrstock et al,[1] in which physicians in private practice in San Francisco were surveyed by telephone, also shows that housestaff physicians are more willing to perform abortion on request than are physicians who have already completed residency training. In addition to spending more time in the hospital, as Wolf pointed out, the residents are also generally younger than and not as far advanced in their medical career as physicians who have already completed their residency training. The medical attitudes of the residents will probably be less strictly formed and more easily modified than attitudes of physicians who have already completed their residency training.

An interesting area for further study concerns some of the origins of ambivalent feelings around abortions. Our general impression from this study was that a distinction is required between negative feelings about the taking of human life, and negative feelings about the sexual activities of the women receiving abortions. The former involves traditional values concerning human life and definitions of when life becomes human and when this human, or potentially human, life can be legitimately taken. The latter involves the attitudes of the medical professional concerning both his own sexuality and the sexuality of the women receiving abortions. It is important that both these attitudes be distinguished so that their influence on medical care can be constructively directed.

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Medical Staff Conference

Progressive Systemic Sclerosis

"Something Old, Something New, Something Borrowed, Something Blue"

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *The first topic for Medical Grand Rounds this morning is that of progressive systemic sclerosis. The subtitle is "Something Old, Something New, Something Borrowed, Something Blue." I guess we shall see whether "something blue" relates to the Raynaud's phenomenon. The case for presentation will be summarized by Dr. James Strauchen.*

Case History

DR. STRAUCHEN:† The patient, a 53-year-old white woman with a long history of scleroderma, was admitted with chief complaint of constipation. Thirty years ago the patient first experienced Raynaud's phenomenon and swelling of the hands. Twenty-two years ago she noted progressive tightening of the skin over the hands and face. Scleroderma was diagnosed at that time, and she was treated with vasodilators. Ten years ago the patient presented with dryness of the eyes and mouth. Results of Schirmer and Rose Bengal tests were positive and Sjögren's syndrome was diagnosed. Three years before the present admission, the patient began to experience progressive difficulty in walking because of right hip pain. A month ago she was admitted to hospital with increased hip pain, severe dental caries and dyspnea on exertion.

On physical examination the patient was emaciated but appeared not to be in acute distress. Vital signs were unremarkable. The skin was taut, shiny and sclerotic, with telangiectasia over the hands, face, lips, and buccal mucosa. On examination of the head, beak deformity of the nose, microstomia and xerostomia were noted. Breath sounds were decreased without dry inspiratory rales. No abnormalities of the heart and abdomen were noted. There was generalized stiffness and wasting of the extremities, ulceration of the distal digits and decreased range of motion of the right hip. No neurologic abnormalities were observed.

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*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine

†James A. Strauchen, MD, Intern in Medicine

The blood cell count was within normal limits and the sedimentation rate was 26 mm per hour. Microscopic examination of the urine showed more than 50 white cells per high power field. A urine culture grew 10^7 colonies of E. coli per ml. Blood urea nitrogen (BUN) and electrolytes were within normal limits. Creatinine clearance was 59 ml per minute. The lupus erythematosus preparation and antinuclear antibodies were negative. The rheumatoid factor was 1:12,800. Arterial blood gases were within normal limits. Pulmonary function tests revealed decreased vital capacity and normal diffusing capacity. An electrocardiogram showed T-wave inversion in the anterior precordial leads. X-ray examination of the chest was within normal limits, but that of the right hip showed severe degenerative joint disease.

Hospital Course

The urinary tract infection was treated with sulfisoxazole. Carious teeth were extracted. Labial biopsy demonstrated lymphocytic infiltration of the minor salivary glands. The patient was evaluated for possible right hip replacement but it was felt that the risk outweighed the potential benefit and she was discharged on a trial of conservative management.

Dr. Smith: *Thank you, Dr. Strauchen. Dr. Robert Siegel will discuss this patient and the general topic of progressive systemic sclerosis.*

Dr. Siegel:* The title of this discussion, "Something Old, Something New, Something Borrowed, Something Blue," was chosen to indicate the topics that I shall touch upon: the history of scleroderma, recent findings, overlap syndromes borrowed from other diseases, and pathogenesis—the reason for the blue of Raynaud's phenomenon. The patient presented here today certainly illustrates several features of this disease which have continued to frustrate internists to this day. She has had a prolonged, relentlessly progressive disease with secondary complications of Sjögren's syndrome and flexion contractures. She is bedridden, and we have a few resources available for her rehabilitation.

The history of scleroderma may date back to Hippocrates,[1] who described a man with generalized pruritus and fixed skin over his entire body. The skin could not be lifted because of its thickness. The first detailed case report is traditionally credited to Curzio of Naples in 1755.[2] He described a 17-year-old woman in whom extensive hardness of the tongue and the skin over her face, eyelids and body had rapidly developed. However, with warm milk, vapor baths, quicksilver and bed rest she recovered completely in 11 months. The exact diagnosis in this case is currently questioned. The absence of Raynaud's phenomenon, the relative sparing of the extremities, and the complete recovery have suggested to Capusan[3] that the patient may have had Buschke's scleredema, a self-limited disease with diffuse or local hardening of the skin following a childhood streptococcal infection. Although the question of historical precedence may be undecided, the disease was certainly well recognized in the 19th century. Sir William Osler concluded that thyroid hormone had no effect in this disease and lamented that patients with scleroderma were doomed to be "encased in an ever shrinking, slowly contracting skin of steel."[4] This quotation focused emphasis on the cutaneous manifestations of scleroderma for a long time. Only in the last 30 years has it been realized that this is a progressive systemic disease as well as a cutaneous one, and the term *scleroderma* (tough skin) only describes a small part of the pathologic change that develops in patients with the disease — progressive systemic sclerosis.

TABLE 1.—*Clinical Classification of Scleroderma*

Localized	
1. Morphea	
2. Generalized Morphea	
3. Linear Scleroderma	
4. Nodular Scleroderma—50 percent Systemic	
Overlap Syndromes	
1. Mixed Connective Tissue Disease ("Lupoderma")	
2. Sclerodermatomyositis	
Systemic Forms	
1. Diffuse Progressive	5 percent
2. Acrosclerosis	95 percent
a. Thibierge-Weissenbach (Raynaud's, Sclerodactyly, Telangiectasia)	
b. CRST (Calcinosis, Raynaud's, Sclerodactyly and Telangiectasia)	

A clinical classification of scleroderma is listed in Table 1. There are several localized forms, including morphea, which can be either a discrete plaque or diffuse morphea involving much of the trunk and extremities. In linear scleroderma, there is a band-like area of fibrosis which is fixed to the

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*Robert C. Siegel, MD, Assistant Professor of Medicine and Orthopedics, and Fellow of the Helen Hay Whitney Foundation

TABLE 2.—*Symptoms Heralding Onset of Scleroderma*

Author	*Tuffanelli*[8]	*Rodnan*[13]	*Poirier*[17]	*Sackner*[12]
Cases	727	95	364	65
Vasospastic (Raynaud's)	48%	37%	70%	28%
Dermal	30%	27%	12%	20%
Arthritic	12%	31%	17%	43%
Dyspnea, Dysphagia, Bloating	10%	5%	1%	9%

underlying structures. There may be atrophy of underlying skin or muscle. In nodular scleroderma, there are whitish elevated nodules, and there is progression to systemic sclerosis in 50 percent of cases. This form is the only localized form with a significant incidence of systemic progression.

Several overlap syndromes are recognized. Most recently, the "mixed connective tissue disease" has been described.[5] Patients with this disease have some features of both systemic lupus erythematosus and scleroderma. They have very high titers (1:100,000) of antibodies to an extractable nuclear antigen (ENA) which is ribonuclease sensitive. In contrast, patients with systemic lupus erythematosus (SLE) may have antibodies against ENA antigens that are not destroyed by ribonuclease.[6] The patients with the mixed disease are clinically characterized by features of systemic lupus, including serositis, Raynaud's phenomenon, active arthritis and high titer speckled antinuclear antibody. They rarely develop renal disease, however. They have swollen digits reminiscent of scleroderma, abnormal esophageal motility and myositis. Frequently, the skin and muscle disease responds to steroids. Patients with "lupoderma" are rather similar to patients with mixed connective tissue disease but are predominantly young females. Patients with sclerodermatomyositis have sclerodermatous skin involvement, inflammatory muscle disease and the typical rash of dermatomyositis.

Of the two systemic forms of scleroderma, the diffuse progressive form is quite rare. It composed 5 percent of cases in the Mayo Clinic experience.[7] In this disease, there is absence of Raynaud's phenomenon, equal male to female incidence and predominate involvement of the trunk. It runs a fulminant course with a five-year survival of approximately 39 percent compared with 70 percent survival in the Mayo Clinic series of the more common acrosclerotic form of progressive systemic sclerosis[8] (PSS). The acrosclerotic form comprises at least 95 percent of cases of PSS. It is the type seen in the patient presented today and in most patients with scleroderma. The term *acrosclerosis* itself implies that there is clinical skin involvement distal to the metacarpophalangeal joints. In the Thibierge-Weissenbach syndrome, telangiectasia develops as well as Raynaud's and sclerodactyly. Since it takes about ten years for calcinosis to develop, this latter syndrome and the calcinosis, Raynaud's, sclerodactyly and telangiectasia syndrome (CRST), probably refer to the same group of patients. Patients who present with the CRST syndrome may have outlived most of the early, serious complications of the disease. However, recently a group of patients with the CRST syndrome and biliary cirrhosis was described.[9] Esophageal and pulmonary involvement also occurs in some cases of CRST syndrome, so there is not total absence of systemic progression but perhaps a slower rate of progression.

The peak age of onset of the acrosclerotic form of scleroderma is between 30 and 50 years with a 3:1 female preponderance. Based on the epidemiologic study by Medsger, there is an annual incidence of 2.7 new cases per million population in Shelby County, Tennessee.[10] The incidence has been found to be as high as 12 per million in other studies, such as the one in Rochester, Minnesota.[11]

Table 2 lists the symptoms with which patients first present to a physician. As might be expected, Raynaud's phenomenon is the leading symptom except in the series reported by rheumatologists, who initially seem to have more patients with nonspecific arthritis referred to them for diagnostic evaluation.[13] Raynaud's phenomenon may be the presenting symptom of 70 percent of the patients. Subsequently, digital swelling and cutaneous induration appear. Initial presentation with gastrointestinal symptoms or pulmonary fibrosis and dyspnea is rare.

Survival in scleroderma is influenced by the type and degree of internal organ involvement. The overall five-year survival in the large Mayo Clinic series was 70 percent and the ten-year survival 58 percent. This included patients with CRST and Thiebierge-Weissenbach syndromes. The recent Veterans Administration study by Medsger related survival rate to type of organ involvement. Renal involvement was the worst prognostic sign: all of 16 patients in whom it occurred were dead within one year. Survival was also poor with cardiac involvement. In the absence of significant internal organ involvement, the seven-year survival was approximately 34 percent. The overall five-year survival rate was 34 percent as compared to that 70 percent reported from the Mayo Clinic. It seems likely that the high mortality was related to the fact that diagnosis was established in the hospital. Certain classes of patients, such as women with mild disease, probably were not represented to as great an extent as they would be in a series drawn from a private practice or the community at large.

In the next section of this discussion, we shall examine individual organ involvement with respect to clinical findings, laboratory findings and pathologic changes. Table 3 was adapted from the controlled autopsy series from Johns Hopkins.[15] The incidence of individual organ involvement was tabulated for a series of 51 cases and compared with matched controls. As expected, there is a very high incidence of cutaneous and esophageal involvement as well as lung and cardiac involvement. Surprisingly, the pericardium was affected in 41 percent. It should be emphasized that these data apply only to patients late in the course of disease, since this was an autopsy study.

TABLE 3.—*Organ Involvement in Scleroderma at Autopsy*[15]

Organ	*Excess over Controls (Percent)*
Skin	98
Esophagus	74
Lungs	59
Kidney	49
Small Intestine	46
Pericardium	41
Muscles	41
Large Intestine	39
Myocardium	26

Cutaneous involvement in PSS can be divided into three phases. Early in the course of the disease the fingers and hands become edematous. This phase may be extremely transient and last for a few weeks, at most. Later, there is the characteristic induration which progresses from the hands up the arms with loss of skin folds and skin appendages. Finally, atrophy of the skin appears, with distal ulcers, induration, loss of knuckle creases, contractures, alteration in pigmentation and telangiectases. Tapering of the digits and loss of soft digital pulp occur in patients with both sclerodactyly and acrosclerosis. X-ray studies of the hands may demonstrate erosions of the distal phalangeal tufts and erosions at the joint margins of the distal interphalangeal or proximal interphalangeal joints. Resorption of terminal phalanges may progress to frank autoamputation of digits. Histologic examination of the skin reveals epidermal atrophy with flattened rete pegs, decreased numbers of capillaries and swollen homogeneous bundles of collagen. There is a loss of normal skin appendages such as sweat glands and hair follicles. A perivascular and dermal mononuclear cell infiltrate frequently is noted on biopsy of specimens taken early in the disease.

Involvement of the joints in scleroderma is quite variable. Patients with significant involvement usually have a positive test for rheumatoid factor. In addition, tendon rubs may be noted during the course of the disease. This morning, the patient being discussed has a left deltoid extensor tendon rub. This may account for some of her pain which was thought to be due to arthritis of that joint. Probably as a result of this inflammatory tendinitis, flexion contractures and thickened tendons develop. Rarely, tendon thickening may result in carpal tunnel or other nerve entrapment syndromes. The pathologic changes in the joints is interesting when compared with those of rheumatoid arthritis. On biopsy, 80 percent of affected joints will be abnormal. There is a synovitis with perivascular mononuclear cells. In contrast to rheumatoid arthritis, cartilage erosions do not occur in scleroderma although bony erosions may. The principal findings are synovial fibrosis as well as fibrinous deposits on tendon sheaths, which are responsible for the tendon rubs detected by auscultation.

Gastrointestinal Involvement

The gastrointestinal tract, beginning at the mouth, is extensively involved in PSS. A finding specific for scleroderma is thickening of the peridontal membranes. In one study,[16] peridontal membrane thickness on dental x-rays in controls was 0.18 to 0.25 mm. In a patient with scleroderma, it was approximately 1.0 mm, a four-fold increase. Continuing down the gastrointestinal tract, approximately 50 percent of patients during the course of their disease develop symptoms related to the esophagus. These may be epigastric burning, dysphagia or frank regurgitation of gastric contents when supine. The symptoms are due to loss of cardioesophageal sphincter tone and the presence of sphincter incompetence when not assisted by gravity.

Characteristically, there is absent peristalsis of the distal third of the esophagus, which can be noted on ciné esophagogram or esophageal motility pressure curves. Esophagrams are abnormal in at least 85 percent of symptomatic patients. The x-ray findings include esophageal dilatation, decreased peristalsis and reflux. In a recent study of 364 patients with PSS,[17] approximately 75 percent of patients with symptoms referable to the esophagus and 25 percent of asymptomatic patients had abnormalities on x-ray study. In 90 percent of symptomatic patients motility studies reveal abnormalities. Gross pathologic findings range from distal inflammation to esophageal erosions secondary to gastric reflux. True stricture formation occurs rarely, and then mostly in patients with hiatus hernia. Histologic examination of the esophagus reveals a thinned to ulcerated squamous epithelial surface. The most striking abnormality is the complete loss of the muscularis mucosa and replacement by fibrous tissue. This replacement occurs with little evidence of inflammation. The longitudinal muscles in the deeper layers are relatively intact. What causes this unique abnormality is not clear, but recent isotopic studies indicated that there is decreased esophageal blood flow that correlates with decreased motility and loss of sphincter tone. Sphincter tone can be partly restored by parasympathomimetic agents that act locally.[18] However, it is not known whether neuronal denervation precedes the decrease in blood flow.

Further along the gastrointestinal tract, the stomach is rarely involved. It becomes atonic in only 1 to 2 percent of cases. The small bowel is frequently involved, and bloating and cramps may develop. Pseudo-obstruction may occur as a result of the stasis and poor peristalis. This may also lead to malabsorption with bacterial overgrowth and deconjugation of bile acids.[19] On x-ray study, one can see decreased bowel motility and dilatation of the third part of the duodenum and distal small bowel, with thickening of transverse mucosal folds. Histologically, specimens from this area are similar to those from the esophagus, showing fibrosis with little inflammation in the muscularis mucosa.

The colon is rarely symptomatic. There are two reported cases of large bowel obstruction due to impaction of fecal material and giant diverticula in the descending colon. The characteristic finding on barium enema is a single wide-mouthed diverticulum in the transverse or descending colon along the antimesenteric or free border. It is due to local atrophy and fibrosis of the muscular layer along that aspect. In the Johns Hopkins autopsy series,[15] 33 percent of patients had these diverticula *in vivo,* but they could not be demonstrated post mortem even by deliberate search. It is probable they collapse very rapidly unless they become infected.

Renal Involvement

The diagnosis of scleroderma renal disease implies a life expectancy measured in months. At present, the risk factors for developing scleroderma kidney are unknown. It has been suggested that previous treatment with steroids predisposes patients to this complication,[20] though it does occur in patients who have never received steroids. There is no correlation with previous proteinuria or hypertension, and the renal failure that usually occurs is an acute oliguric form with rapidly rising creatinine, unremarkable renal sediment and normal sized kidneys on x-ray films. Frequently, there is associated severe refractory hypertension of rapid onset, but normotensive renal failure with similar clinical and histologic findings has been demonstrated.[15] Renal angiographic findings include tortuous, irregular interlobular arteries with retention of dye in the arterioles for up to 10 seconds.[21] Similar findings have been noted with a variety of renal lesions, including arteriolar nephrosclerosis, and after the injection of catecholamines.[21] At pathologic examination, the kidneys are of normal size or slightly swollen. There are petechial cortical infarcts which may be pale or hemorrhagic. Postmortem corrosion preparations after arterial injections reveal almost total obliteration of arteries beyond the intralobular vessels.[22] The characteristic microscopic findings are fibrinoid necrosis of the intralobular arteries, afferent arterioles and sections of glomerular tufts. There is intimal proliferation in the intralobular arteries with reduplication of the internal elastic membrane and thickening and reduplication of the glomerular basement membrane. Figure 1 illustrates the massive fibrinoid necrosis of the arterial system that can occur.

Turning briefly to other organ systems, one notes that cardiac involvement occurs in nearly 50 percent of cases. The onset of congestive heart failure is a bad prognostic sign and usually becomes a recurrent problem. The physical findings reflect the presence of mild pulmonary hypertension with an increased pulmonic second sound and an atrial gallop in 50 percent of cases with congestive failure. Pericardial friction rubs are occasionally noted, but there is much less clinic-

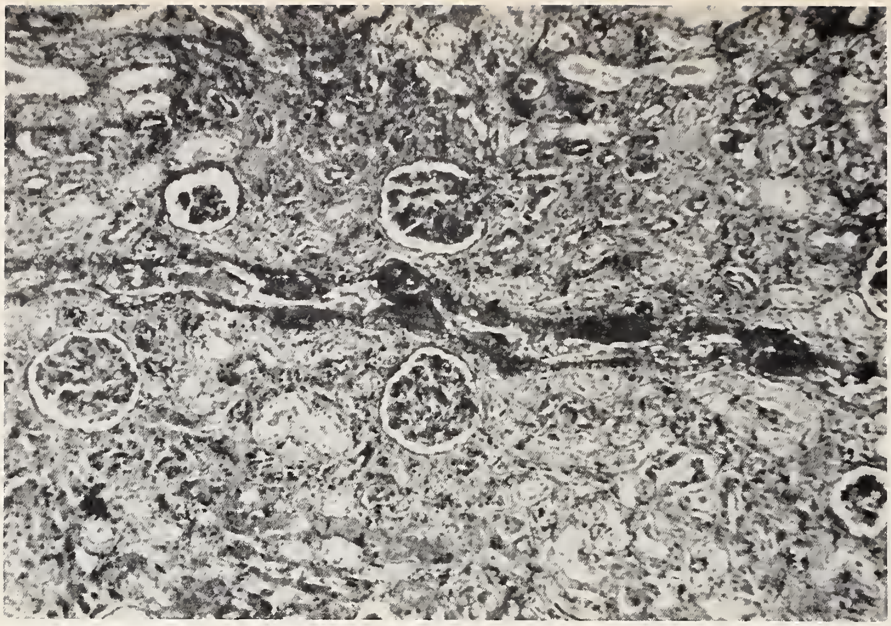

Figure 1—Low power hematoxylin and eosin stained section of renal cortex from a patient with scleroderma kidney. There is fibrinoid necrosis of the entire arterial wall of an intralobular artery and of segments of glomeruli to which it sends afferent arterioles.

TABLE 4.—*Theories of Pathogenesis of Scleroderma*

1. Abnormality of Tryptophan Metabolism
2. Primary "Immunologic" Abnormality
3. Primary Connective Tissue Abnormality
4. Primary Vascular Disease

ally apparent involvement of the pericardium than is found at autopsy. Histologically, there is replacement of muscle fibers with mild fibrosis. Thickening of the free edge of the tricuspid valve has been reported.[15]

As the disease progresses, several symptoms referable to the lungs may develop. Patients become dyspneic and develop a dry, non-productive cough. Clinically, there are fine, dry inspiratory rales, and on x-ray studies progressive fibrosis appears at the bases. Occasionally this may progress to frank honeycomb lungs. The pathologic changes include alveolar and interstitial fibrosis as well as intimal proliferation and medial hypertrophy in the small arteries, similar to that seen in the kidney.

Pathogenesis

Several themes have recurred in this review of organ pathology, and these may serve as a focus for a discussion of the pathogenesis of scleroderma. There seems to be primary fibrosis without much inflammation and at times small arterial involvement out of proportion to the degree of fibrosis. There are several suggestions for the cause of these changes, and some are summarized in Table 4. An early suggestion was an abnormality of tryptophan metabolism. Tryptophan may be metabolized to either niacin or serotonin by different pathways. Ordinarily, only 1 percent of tryptophan is metabolized to serotonin. Patients with carcinoid syndrome may develop right sided endocardial fibrosis, and scleroderma and retroperitoneal fibrosis have developed in some cases of carcinoid syndrome. Serotonin increases the synthesis of connective tissue *in vitro*. After a tryptophan load, patients with scleroderma excrete decreased amounts of niacin and increased kynurenine and hydroxykynurenine, both intermediates in the niacin pathway. This suggested that, in the tryptophan pathway, enzymes which metabolized kynurenine and hydroxykynurenine were inhibited.[23] If such a block in the niacin pathway did exist in scleroderma, more tryptophan might be metabolized to serotonin, which in turn might lead to increased fibrosis. Although this is an interesting line of reasoning, it is not being pursued at present.

Immunologic abnormalities have been noted in PSS. On laboratory examination of patients with scleroderma, approximately 50 percent have positive antinuclear antibodies, usually with a speckled or nucleolar pattern; only 4 percent have positive LE preps. Frequently, there is a nonspecific broad-based hypergammaglobulinemia. There are no demonstrated correlations between the course of the disease and any specific immunologic abnormality.

Because of the apparent increase in connective tissue, there have been extensive studies of collagen metabolism in this disease. Recently, biopsy of affected skin from patients with scleroderma has shown it to have increased proline hydroxylase activity.[24] This enzyme is required for the synthesis of collagen. It specifically hydroxylates proline residues in the completed collagen molecule. An apparent increase in fetal collagen at affected sites has been described in patients with scleroderma.[25] An electron microscopic comparison of collagen fibrils was made, using biopsy specimens from patients with scleroderma and from normal adult and human embryonic skin. In normal adults there were collagen fibrils 1,400 angstroms in diameter. In patients with scleroderma, there was a pronounced shift to very thin fibrils, with maximum diameters of 400 to 500 angstroms. Fibrils with these smaller diameters were noted in normal human embryo and fetal pig skin. On electron microscopy with negative staining, these small fibrils had a characteristic beading every 640 angstroms. The biochemical significance of these findings is not known, but normal collagen has characteristic bands that repeat every 640 angstroms. These bands may be specific for a certain part of the molecule.

When studied in culture, fibroblasts from affected skin in patients with scleroderma have increased collagen synthesis.[26] As yet, these studies have not defined the type of collagen being synthesized in excess by the affected fibroblasts. There also was an increased hexosamine production in the fibroblast cultures. This had been noted earlier in the studies of whole skin. The explanation for these observations is not clear. One might speculate that both fetal tissue and affected skin in scleroderma are relatively anoxic. Perhaps higher oxygen concentrations are required for synthesis of fibrils of the adult size. Certain enzymes required for collagen synthesis, such as proline hydroxylase and the cross-linking enzyme, are oxygen-dependent.

In the pathologic changes reviewed earlier, vascular lesions were observed in a wide variety of organs. Currently, the most popular theory of pathogenesis is that a primary vascular lesion[27] leads to the other changes. Capillary abnormalities have been noted for a long time. Normally, there are approximately 30 capillary loops per cubic millimeter at the nailfold.[26] In scleroderma, pronounced drop-out of the loops occurs so that as few as one loop per cubic millimeter may remain. The loops also change in appearance; the remaining ones enlarge and the efferent loop becomes dilated with stasis and sludging. The loss of capillaries and the sluggish blood flow precede the typical cutaneous changes, and larger blood vessel involvement preceding visceral functional impairment has also been documented. Arteriolar abnormalities with intimal proliferation, medial hypertrophy, reduplication of the basement membrane and endothelial fibrin deposition have been observed in the lungs before the onset of pulmonary fibrosis and restrictive lung disease. These observations imply that a primary small blood vessel abnormality may be the principal lesion in scleroderma. The connective tissue abnormalities that follow may occur secondary to decreased blood flow and relative anoxia. Further investigation should be able to test these speculations.

Management of Scleroderma

Finally, the most frustrating problem of all must be addressed—the management of scleroderma. Although dramatic cures have been claimed for many therapeutic maneuvers from Curzio to the present, there is no widely accepted treatment for the underlying disease. Therefore, the major emphasis in treatment should be to prevent possible complications.[29] All patients should be treated with a hiatus hernia regimen to prevent gastroesophageal reflux since 25 percent of even the asymptomatic patients have reflux. As the disease progresses, reflux and the late complications of stricture will develop in an even higher proportion. This is particularly likely if a hiatus hernia remains untreated.[17] Patients should avoid smoking because nicotine absorbed through the digital skin precipitates vasospasm and may lead to digital ulcers and increased Raynaud's phenomena.

Malabsorption may respond to oral tetracycline and, thus, is also a potentially treatable complication.[19] Frequent physical therapy should be encouraged to prevent contractures and to increase range of motion.

Raynaud's phenomenon and digital ulcers can be quite disabling. A wide variety of treatment has been tried. Sympathectomy has been used in the past, but it is no longer indicated in patients with PSS.[30] Transient palliation followed by rapid return of symptoms has been the experience. Of the various drugs that have been tried, oral reserpine is the best-studied. Increased digital capillary blood flow and healing of digital ulcers as the capillary blood flow increases have been documented in patients given oral reserpine. Some patients have required as much as 1 mg of reserpine for benefit, however, and many may not be able to tolerate this dose.[31]

Because of the difficulties encountered with the use of oral reserpine, intra-arterial reserpine has been used with reported healing of digital ulcers and decreased frequency of Raynaud's disease. Success rates of approximately 70 percent with this mode of administration have been reported, and side effects are minimized.[32] However, a portion of this effect is probably placebo since a double blind study comparing intra-arterial reserpine with saline solution had an overall improvement rate of 63 percent with similar responses to either injection.[33]

Recently, a patient with fulminant scleroderma kidney has been treated with hemodialysis and transplantation.[34] Following nephrectomy, hypertension became easily controlled. This patient is doing well approximately one year after transplantation. Perhaps, greater availability of these scarce resources will allow scleroderma patients with this lethal complication to survive and have additional productive years.

Evaluation of the effect of systemic treatment in this disease is particularly difficult because of its variable and prolonged course. Since the principal morbidity from the disease results from visceral involvement, therapeutic measures should be assessed with respect to their ability to halt visceral progression. Most of the drugs reported in the literature have been shown to promote only cutaneous improvement. However, prolonged treatment with chlorambucil (0.1 mg per kg of body weight daily) for up to one year has been reported to improve pulmonary function in six of eleven patients in one study, and all eleven patients gained weight and noted improved range of motion in their hands.[35] As yet, these results have not been confirmed by other investigators. The great variability of disease activity, of degree of visceral involvement, and of prognosis depending on type of visceral involvement emphasizes how difficult a drug trial would be to perform. It might not be possible to draw definite conclusions from a study lasting less than four to five years. Until well controlled studies that consider the long natural history of the disease are available, it would be well to direct therapy at the potentially remediable local problems rather than develop further anecdotal experiences for a wide range of systemic agents with severe side effects and little documented efficacy.

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Phagocytic, Opsonic and Immunoglobulin Studies in Newborns

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Despite improved diagnostic and therapeutic measures, neonatal septicemia continues to be a major clinical problem. Improvement in the management of the septic neonate should result from application of the increasing information being learned of the neonatal host defense mechanisms. The earlier concept that the neonate was "immunologically null" can now be discarded. Evidence summarized in this review has established that the neonate can marshal an immune response to most antigens and infectious agents.

A further major advance in recent years has been in understanding of the inflammatory response in the neonate, which includes such activities as chemotaxis, phagocytosis and bactericidal killing of ingested bacteria by phagocytes.

UNDERSTANDING OF THE MEANS by which the normal human neonate maintains resistance against micro-organisms has assumed great clinical significance in recent years. This reflects growing understanding of the functional status of neonatal host defense mechanisms. Contrary to earlier beliefs, it is now clear that the normal neonate is not "immunologically null" but has a variety of "specific" and "non-specific" mechanisms available for combatting foreign micro-organisms. In this review, we discuss the current understanding of three important aspects of neonatal host defenses — immunoglobulins, phagocytes and opsonins.

First let us consider the development of the humoral immune response in the neonatal period, with particular emphasis on alterations of the immunoglobulins in health and disease.

Immunoglobulin Synthesis in the Fetus

In human fetuses synthesis of immunoglobulin M (IgM) has been detected as early as ten and a half weeks,[1] by tissue culture of fetal organs in the presence of radiolabelled amino acids followed by radioimmunoelectrophoresis, primarily in the spleen but in other lymphoid organs as well. IgG synthesis was detected at 12 weeks of gestation and IgA synthesis by 30 weeks.[1]

Van Furth et al[2] detected IgG- and IgM-

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fluorescing cells in lymphoid tissue in human fetuses by 21 weeks. Lawton and coworkers found IgM, IgG and IgA surface determinants by immunofluorescence (B cells) in peripheral blood, bone marrow, liver and spleen by eleven and a half weeks.[3] By 14 weeks the distribution of immunoglobulin-staining cells is equivalent to that found in adult tissues. However, cells with cytoplasmic immunoglobulin (those synthesizing immunoglobulin) were not found in early fetuses and do not appear until the time when endogenous immunoglobulin synthesis is occurring.

Although IgG synthesis does not occur until at least 12 weeks, IgG can be detected in the serum of the fetus as early as 38 days, as the result of passive transfer from the mother.[1] Serum IgM is detectable occasionally as early as 17 weeks and is regularly detectable by 30 weeks. Although IgA may be present in the fetal serum in trace quantities as early as six and a half weeks of gestation, it presumably is of maternal origin; IgA may be present more frequently at this time than in the later weeks of gestation, since IgA synthesis is not usually established until close to or after the time of birth.

In sum, the precursor cells of immunoglobulin synthesis (B cells), the synthesizing cells (plasma cells), and the serum immunoglobulins are present in the human conceptus and fetus, and appear in the order IgM, IgG, and IgA, similar to the sequence of the appearance of antibody classes following antigenic stimulation.

Antibody Synthesis in the Newborn

Although the newborn infant has developed the cellular apparatus necessary for active antibody synthesis, it is for the most part dormant at birth. After stimulation, a sluggish response is often noted, particularly to certain antigens; further, the response is often inhibited by maternal transplacental antibody.

Natural Antibodies

Natural antibodies, (antibodies present without active immunization) notably the isoagglutinins, are not synthesized well by the newborn, presumably due to lack of intrauterine antigenic challenge.[4] IgG natural antibodies from the mother will of course be present as a result of transplacental passage. A few investigators have detected endogenously-synthesized natural antibodies in newborn sera. Thomaidis et al[5] found mercerpto-ethanol-sensitive isoagglutinins (and therefore presumably IgM) in 36 of 59 full-term infants, indicating some natural antibody production. Adinolfi[6] found an anti-I cold agglutinin in 14 of 23 cord sera specimens; this was an IgM antibody, indicating endogenous antibody production. Mellbye[7] noted an IgM antibody in all of 20 specimens of cord sera which agglutinated trypsinized-compatible human erythrocytes. Epstein et al[8] found that nearly all cord sera contained an IgM antibody which agglutinated erythrocytes coated with heated Bence-Jones proteins (light chain determinants). All of these IgM antibodies may occur as the result of intrauterine antigenic stimulation which leads to IgM synthesis and some degree of cross-reactivity with these specially-treated erythrocytes.

Inhibition by Maternal IgG Antibody

Transplacentally acquired maternal antibody has a pronounced inhibitory effect on active antibody formation in the newborn period.[9] For examples, infants with passively acquired diphtheria antitoxin or poliomyelitis antibodies have decidedly diminished response to diphtheria toxoid[10] or inactivated poliomyelitis vaccine[11] respectively. Newborn premature and term infants with high levels of passive flagellar agglutinins to Salmonella did not respond at all; infants with moderate titers responded suboptimally; infants without passive agglutinins responded as well as adults to Salmonella vaccine.[12] The specific immunosuppressive effect of maternal antibody is the rationale for delaying measles and rubella vaccination until after six to twelve months of life. For certain powerful antigens (tetanus, for example), the inhibition can be overcome by larger or more frequent immunizations or by the use of adjuvants.[9]

Response to Active Immunization

Administration of antigen to an immunologically immature subject has the potential risk of inducing immunologic tolerance (non-reactivity) rather than immunization. This is exceedingly rare in humans although Provenzano et al[13] noted that 21 of 22 infants given pertussis vaccine during the first 24 hours of life had inadequate response or none at all; further the response to reimmunization in 75 percent of these infants was inadequate up to the age of 15 months, suggesting some degree of tolerance.

Most studies indicate that the newborn responds to injected antigens but to a lesser degree than older infants and adults. This is true even in the absence of passive maternal antibodies and with a variety of antigens including diphtheria toxoid,[14] inactivated poliomyelitis vaccine,[15] pertussis whole bacterial vaccine[16] and the O antigen of Salmonella typhosa.[12]

There are exceptions to this statement. Smith et al[12] found that the antibody response to the H antigen of Salmonella typhosa was equal in premature and term infants and that their responses were almost as good as in the adults. Osburn et al[17] found that antitoxin levels following the administration of absorbed tetanus toxoid to infants less than two weeks of age were not significantly different from those produced by older infants.

Even when the antibody response of the newborn is adequate, it may differ qualitatively from that of older infants and adults. Smith et al[12] showed that newborns given Salmonella vaccine have IgM flagellar agglutinins exclusively for 20 to 30 days, in contrast to older subjects who have IgM agglutinins during the first week, followed by the appearance of IgG agglutinins.

Extrauterine life stimulates the maturation of the immune system. Dancis et al[18] showed that only one of seven premature and one of eight term newborns responded to diphtheria toxoid; however, seven other prematures immunized at their estimated term birth date (and thus equivalent in age to the term newborns) all responded to diphtheria toxoid. Rothberg[19] showed that the antibody response of premature infants to oral bovine serum albumin was as good as that of term infants, indicating that the interval since birth is more important than the size or somatic maturation.

Inhibition by Breast Milk Antibodies

Maternal breast milk antibodies may inhibit antibody production to orally administered live poliovirus vaccine by inhibiting viral colonization of the gastrointestinal tract.[20] Colostrum may be especially effective because of its higher immunoglobulin content. This effect may be particularly important in the developing countries, where breast feeding is generally prolonged.

Summary

The newborn infant has the ability to synthesize antibodies when stimulated by antigens, but the response generally is less vigorous than in older infants and adults. Further, the antibody response in newborns may differ qualitatively in prolongation of the IgM response. The age of the infant is better correlated with a strong antibody response than is the maturity of the infant, since the bacterial colonization of the gastrointestinal tract which occurs at the time of birth is the major stimulus for the maturation of the antibody system.

Passive Immunity in the Newborn

The infant passively receives IgG antibodies via the placenta; if breast-fed, he receives secretory antibodies (which are not absorbed) via the oral route. The newborn is protected by IgG maternal antibodies to those disorders in which immunity is associated with long-term persistence of circulating IgG antibody (such as measles, rubella, meningococcal infections, streptococcal disease and H. influenzae infection); some protection against certain other infections (such as vaccinia, varicella, pertussis, tetanus, diphtheria) may also result but, since high titers of protective IgG antibodies do not persist, only recently infected or immunized mothers provide protection to their infants. Certain maternal antibodies to antigens of Gram-negative organisms such as E. coli and Salmonella reside within the IgM class and do not cross the placenta, so that the infant does not receive all of the mother's antibodies to these organisms. Gitlin et al[21] postulated that this deficiency of IgM may be responsible, at least in part, for the unusual susceptibility of newborns to infection with Gram-negative organisms. However, there are IgG antibodies to somatic antigens of these Gram-negative organisms which do cross the placenta and provide sufficient protection for most infants.[22]

In some instances, it is a distinct advantage to have maternal IgM antibodies excluded from the infant; for example, the presence of maternal IgM isoagglutinins (natural anti-A and anti-B) in the infant would result in ABO hemolytic disease in every ABO incompatible maternal-newborn pair.

The passive secretory antibodies ingested by the breast-fed infant inhibit the growth of certain bacteria (for example, E. coli) and viruses (enteroviruses for example) in the gastrointestinal tract. This may have significant survival advantage, particularly in the developing countries. A decreased intake of breast milk may predispose to neonatal septicemia. Winberg and Wessner, in Sweden, noted this;[23] since the decreased intake occurred before the symptomatic period, it was not due simply to poor suckling by sick children.

Immunoglobulin Levels in Fetus, Newborn, and Neonatal Periods

Detailed study of the immunoglobulin levels in health and disease has been greatly facilitated by the development of the radial immunodiffusion method which permits accurate rapid quantitation of serum immunoglobulins from small quantities (less than 1 ml) of serum. Commercial immunodiffusion kits with agar plates and standards are available from several companies.*

IgG

IgG is present in the serum of the human embryo as early as 38 days of gestation despite the absence of IgG-synthesizing cells until three months.[24] IgG levels remain below 100 mg per 100 ml (5 to 10 percent of maternal level) until about 17 weeks of gestation, at which time the IgG increases gradually; at term (40 weeks) the fetal IgG level usually exceeds the maternal IgG level by 5 to 10 percent. Kohler and Farr[25] studied 46 maternal-cord paired specimens and noted a mean maternal IgG of 1,512 mg per 100 ml and a mean cord IgG of 1,260 mg per 100 ml. Gitlin described a rather abrupt onset of maternal-fetal transfer at 22 weeks, so that most fetuses of 25 to 40 weeks had IgG levels equivalent to the maternal level.[1,24] Other investigators,[26-29] including ourselves,[30] have demonstrated a gradual increase of fetal IgG levels, beginning at about 25 weeks; we recorded IgG levels at 26-27 weeks of 330 ± 61 (mean ± 1 standard deviation), at 32-33 weeks 556 ± 107 mg per 100 ml, at 36-37 weeks 823 ± 135 mg per 100 ml and at term (40-41 weeks) 937 ± 175 mg per 100 ml (Chart 1). This increase allows an estimation of gestational age by the cord blood IgG level. Nearly all of the cord IgG is of maternal origin; however, Martensson and Fudenberg,[31] by assaying genetic gamma-globulin (Gm) types, detected trace quantities of endogenously synthesized IgG in cord blood.

Gitlin has shown that the materno-fetal placental transfer of IgG is under the influence of two distinct mechanisms.[24,32] The first is a passive transfer, in which the fetal IgG level is proportional to the maternal IgG level. This mechanism undergoes maturation with increasing gestational age to permit increased amounts of IgG to cross the placenta with increasing fetal maturation. The second is an enzymatic mechanism which actively transfers IgG from mother to fetus. Because this enzymatic mechanism is inhibited at high maternal IgG levels and is increasingly activated at low maternal IgG levels, it acts as a normalizing influence on IgG levels; infants born to mothers

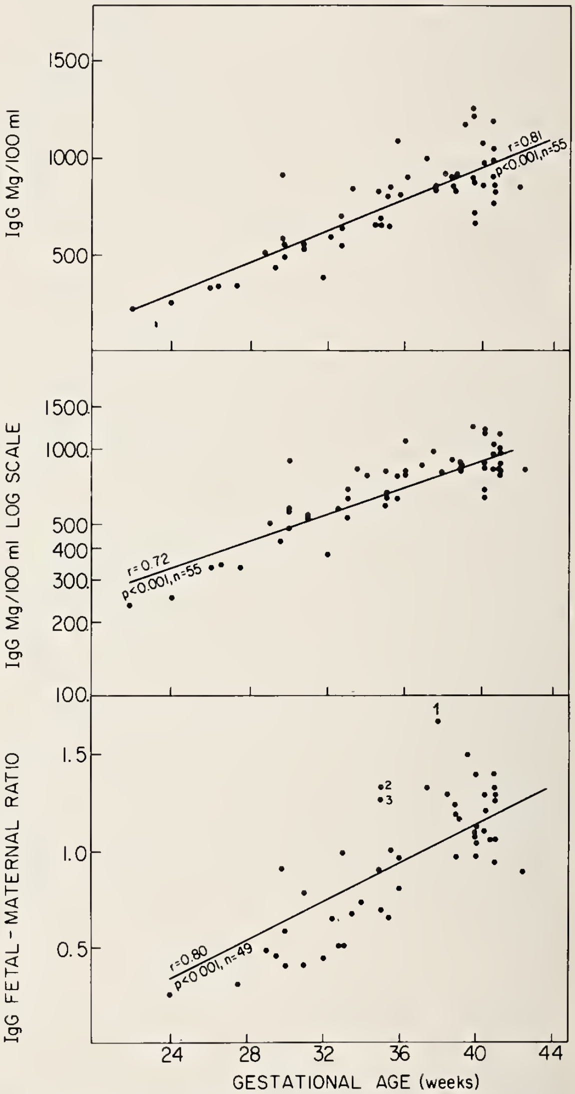

Chart 1.—Correlation of gestational age with (top) serum IgG concentration, (middle) logarithm of serum IgG concentration, and (bottom) fetal-maternal ratio of IgG in appropriate-for-gestational age infants. Correlation of IgG with birth weight was almost as good ($r = +0.791$, $p < 0.001$, $n = 55$) as was the correlation of fetal-maternal ratios with birth weight ($r = +0.768$, $p < 0.001$, $n = 49$). Cases 1-3 in the bottom figure illustrate inceased active placental transport of IgG when maternal IgG is low. **Case 1:** maternal IgG 500 mg per 100 ml, fetal IgG 805 mg per 100 ml; **Case 2:** maternal IgG 498 mg per 100 ml, fetal IgG 594 mg per 100 ml; **Case 3:** maternal IgG 498 mg per 100 ml, fetal IgG 632 mg per 100 ml. (Reprinted with permission from Hyvarinen, et al: J Pediatrics 1973, In Press.)

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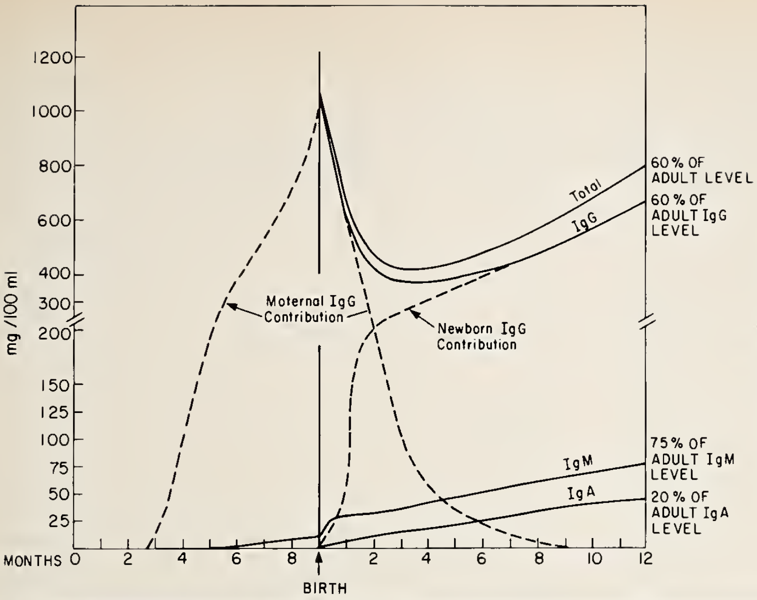

Chart 2.—Immunoglobulin (IgG, IgM and IgA) levels in the fetus and infant in the first year of life. The IgG of the fetus and the newborn infant is solely of maternal origin. The maternal IgG disappears by the age of 9 months, by which time endogenous synthesis of IgG by the infant is well established. The IgM and IgA of the neonate are entirely endogenously synthesized, since maternal IgM and IgA do not cross the placenta.

TABLE 1.—*Levels of Immunoglobulins in Sera of Normal Subjects, by Age*

	IgG		*IgM*		*IgA*		*Total Immune Globulin*	
Age	*mg/100ml*	*Percent of Adult Level*	*mg/100ml*	*Percent of Adult Level*	*mg/100ml*	*Percent of Adult Level*	*mg/100ml*	*Percent of Adult Level*
Newborn ..	1,031±200*	89±17	11± 5	11± 5	2± 3	1± 2	1,044±201	67±13
1- 3 mo ..	430±119	37±10	30±11	30±11	21±13	11± 7	481±127	31± 9
4- 6 mo ..	427±186	37±16	43±17	43±17	28±18	14± 9	498±204	32±13
7-12 mo ..	661±219	58±19	54±23	55±23	37±18	19± 9	752±242	48±15
13-24 mo ..	762±209	66±18	58±23	59±23	50±24	25±12	870±258	56±16
25-36 mo ..	892±183	77±16	61±19	62±19	71±37	36±19	1,024±205	65±14
3- 5 yr ...	929±228	80±20	56±18	57±18	93±27	47±14	1,078±245	69±17
6- 8 yr ...	923±256	80±22	65±25	66±25	124±45	62±23	1,112±293	71±20
9-11 yr ...	1,124±235	97±20	79±33	80±33	131±60	66±30	1,334±254	85±17
12-16 yr ...	946±124	82±11	59±20	60±20	148±63	74±32	1,153±169	74±12
Adults	1,158±305	100±26	99±27	100±27	200±61	100±31	1,457±353	100±24

Values shown above were derived from measurements made in 296 normal children and 30 adults. Levels were determined by the radial diffusion plate method using specific rabbit antisera to human immunoglobulins. Stiehm and Fundenberg, Pediatrics 37:715-727, 1966.

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*One Standard Deviation.

with high or low IgG levels tend to have near normal IgG levels.

The postnatal changes in IgG are ilustrated in Chart 2 and Table 1. Levels of IgG fall rapidly for the first three months of life, with a half-life of 25 days. IgG levels reach a low point at age 4 to 6 months (see Table 1). After this, as neonatal synthesis is initiated, IgG levels gradually increase so that the IgG levels by one year of age average about 60 percent of the adult level. Significant neonatal IgG synthesis does not occur until about the third month of life but is well established by age six months.

Since IgG makes up 70 to 80 percent, the total immunoglobulin level largely reflects the IgG level; thus there is a physiologic hypogammaglobulinemia in all infants at age four to six months.

As was previously noted, the level of IgG of cord blood in term infants usually exceeds the maternal level, usually by a factor of 1.2 with a mean maternal-fetal difference of 252 mg per 100 ml.[25] This active transport of IgG may account for the higher level of specific antibodies in the cord sample of paired maternal-cord sera, even in the absence of fetal antibody synthesis.

There are no sex differences in the cord and neonatal levels of IgG or other immunoglobulins.[33,34] Females may have higher levels of IgM after age 8.[34,35]

Fetally synthesized IgG may traverse from infant to mother. Fudenberg and Fudenberg[36] reported the development of an anti-Gm antibody in a woman during pregnancy with specificity toward her infant's Gm type; they postulated that maternal

IgG anti-Gm antibodies in the fetal circulation could result in physiologic hypogammaglobulinemia. Nathenson et al[37] did not find more abnormally low IgG levels in infants of 28 mothers with anti-Gm antibodies; however, only one infant had a significant anti-Gm titer in the cord blood.

IgG Subclasses

There are four subclasses of IgG. They are IgG1, IgG2, IgG3, and IgG4. Each has unique antigenic, metabolic, and antibody properties, and they make up 65, 23, 8 and 4 percent of normal adult IgG respectively.[38] These subclasses were originally defined by antisera to different IgG myeloma proteins, made specific for a particular myeloma IgG by cross absorption. Each IgG subclass contains specific genetic gamma-globulin factors.

Wang et al[39] reported a decrease in the placental transport of IgG2, with the result that neonates have a relative deficiency in this subclass; this would be of clinical significance since IgG2 contains many antibodies to polysaccharide antigens. They also noted an IgG heavy chain not present in adult IgG, and suggested that there was a new subclass of IgG which is specific for the fetus and is endogenously synthesized. They termed this IgF (for fetal gamma-globulin). It must be pointed out that their studies were done on pooled neonatal and adult sera rather than individual specimens.

Morrell et al[40] re-studied the IgG subclass levels on 115 maternal and 128 fetal sera, most of which were maternal-fetal pairs; they did not find a deficiency of IgG2 in cord blood. They noted low fetal:maternal ratios for all four subclasses up to the 16th gestational week, and then a gradual uniform increase with increasing gestational age for all subclasses. In the last weeks of pregnancy, ratios exceed 1:1, in keeping with the findings of Kohler and Farr.[25] They concluded that all four subclasses are transported equally well across the placenta. Further, the presence of IgG2 in cord blood samples was confirmed by assays for Gm (23), a genetic marker for IgG2; in all instances in which the maternal sera had Gm(23) activity, the corresponding cord sera also contained Gm (23) of equal activity.

These investigators[41] also studied the changes of IgG subclass levels in the first two years of life. As can be seen in Table 2, there was considerable heterogeneity among the subclasses. During the first month of life, levels of all the IgG subclasses decrease steeply but IgG3 falls off most rapidly, reaching a low point by 30 days, in keeping with the more rapid catabolism of this subclass (seven days) compared with the others (20 to 25 days).[42] IgG3 levels then increase rapidly to approach adult levels by age three months. IgG1 levels decrease steeply during the first month and then more slowly for the next two months, indicating the onset of IgG1 synthesis, as early as one month. IgG1 levels reach a low point at age three months, increase significantly by age four months and attain normal adult values by age eight months. IgG2 levels fall at a uniform rate until age three months, and then gradually increase. IgG4 levels show considerble fluctuation during the first year and reach a low point at age 12 months.

TABLE 2.—*Development of the Serum Concentrations of the IgG Subclasses*

		Mean ± 1 Standard Deviation (mg/100 ml)			
Age	*No. of Sera*	*IgG1*	*IgG2*	*IgG3*	*IgG4*
10 days ..	7	594±211	256± 52	56±14	29±24
20 days ..	12	521±215	227± 36	39± 8	18± 9
30 days ..	13	425±127	175± 58	30±10	21±14
2 mo ...	11	383±172	153± 53	31±12	11± 5
3 mo ...	12	332±181	91± 44	45±17	13± 8
4 mo ...	10	424±207	110± 39	47±17	10± 6
8 mo ...	10	659±277	147± 56	51±27	12± 9
12 mo ...	6	653±190	160± 75	53±26	7± 4
24 mo ...	14	652±182	166± 41	45±10	25±20
20 yr	108	663±170	322±108	58±30	46*

Modified, with permission, from Morell et al, J Pediatrics 80: 960-964, 1972.

*Distribution assymetric.

IgM

Most newborns beyond 30 weeks of gestation have low but detectable IgM in their cord serum. Since IgM does not cross the placenta, this indicates that IgM synthesis begins early in fetal life, earlier than any other immunoglobulin class. Buckley et al[45] reviewed the results of seven studies of cord blood IgM levels and found that mean levels varied from 5.8 to 15.8 mg per 100 ml and the two standard deviation limits levels varied from 1 to 10 mg per 100 ml (lower limit) to 12.9 to 27.4 mg per 100 ml (upper limit). We utilize a mean of 10 mg per 100 ml with an upper limit of normal (+2 SD) of 20 mg per 100 ml.[44] Small quantities of IgM are found in nearly 100 percent of cord blood specimens from viable infants.[33,45,46] Other observers report no detectable IgM in 6[47] to 25 percent[29] of cord specimens. Differences between the various studies can be attributed in large part to the sensitivity of the method used.

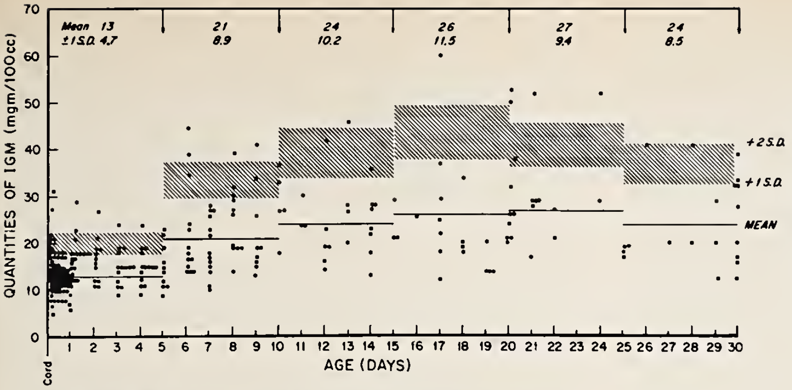

Chart 3.—Serum IgM levels in 175 uninfected newborns during the first 30 days of life. Levels above the shaded area are greater than 2 standard deviations above the mean and are considered abnormally elevated. (Reprinted with permission from Blankenship, et al: J Pediat 75: 1271-1281, 1969.)

The IgM levels in viable premature infants usually are slightly lower than in term infants but not in any predictable fashion.[26,27,29] Further, the proportion of infants with no detectable cord IgM is increased with decreasing gestational age.[29]

Absence of cord IgM has no known clinical significance. In contrast, and as discussed in the next section, an elevated cord IgM level has considerable clinical significance, since it indicates intrauterine antigenic stimulation, often the result of intrauterine infection.

Some of the IgM in cord sera may be in the form of 7S IgM—that is, slowly sedimenting, low molecular weight IgM. Perchalski et al[48] found 7S IgM in six of nine normal cord sera and two of four VDRL-positive cord sera. The contribution to the total IgM and the significance of this 7S IgM is not known; however, 7S IgM has been described in patients with systemic lupus erythematosis, ataxia telangiectasia, dysgammaglobulinemia type I, Waldenstrom's macroglobulinemia, and lymphoma.[49]

IgM synthesis increases rapidly after birth and IgM is the chief immunoglobulin synthesized in the first months of life.[33,34] Buckley et al[43] found that sera from three- and four-day-old infants had significantly higher IgM levels than did cord serum. The second half of the first week of life is a period of rapid rise of IgM levels,[34] probably a result of the antigenic stimulation of gastrointestinal colonization. An exaggeration of this response may occur in the presence of infection acquired at or shortly after birth.[50] As may be noted in Chart 3, IgM levels in normal infants increase rapidly until age 20 to 25 days, then level off or decrease slightly during the next several weeks, only to increase again in the third month of life. The IgM levels at age six months are about 50 to 60 percent of adult levels and 70 to 80 percent by age one year. Adult levels are generally achieved by age two.

IgA

IgA does not cross the placenta and due to a delay in the onset of IgA synthesis, IgA is often not detected by clinical methods in cord blood specimens. Fulginiti et al found IgA in only one of eighteen cord sera specimens by Oudin tube method;[50] Brasher and Hartley found IgA in 30 of 97 specimens of cord sera by immunoelectrodiffusion;[45] Stiehm and Fudenberg found IgA in seven of twenty-two specimens by radial immunodiffusion.[33] When detectable, cord IgA levels usually are 1 to 5 mg per 100 ml. During a maternal-fetal leak IgA levels may be considerably higher (>10 mg per 100 ml), often higher than the IgM level.[44] IgA begins to appear in neonatal sera at about day 15 in most infants (range 5 to 23 days). Levels increase slowly, reaching about 30 mg per 100 ml (15 percent of adult mean) by age six months, and 60 mg per 100 ml (20 to 25 percent of adult mean) by age one year.[32,33] Adult levels may not be attained until adolescence.

IgA may occasionally pass from the mother to the infant via the placenta in trace quantities. Vyas et al[52] described one newborn whose cord serum had anti-IgA antibodies with maternal specificity, suggesting *in utero* sensitization. These same workers found that 15 percent of mothers of recently delivered infants had anti-IgA antibodies, possibly a result of sensitization to fetal IgA following a fetal-maternal leak. Mothers with selective IgA deficiency may be especially susceptible to such *in utero* sensitization.[53]

Secretory IgA

IgA is the chief immunoglobulin of exocrine gland secretions; it is present in a molecular configuration known as secretory IgA which has a larger molecular weight (400,000) than serum IgA and an additional antigenic piece, the secretory component, synthesized by glandular epithelial cells.[54] Since secretory IgA is synthesized locally rather than transported from the serum, there often is not good correlation between serum and secretory IgA levels.

IgA is first detected in the tears of newborn infants between ten and 20 days of age; it was present in the tears of most infants before the serum had detectable IgA.[55] Haworth and Dilling[56] found IgA appearing in the saliva initially at age two to three weeks, usually a few days before its appearance in the serum. In contrast, IgG is usually present in tears and saliva at birth but its origin (fetal or maternal) is in doubt.[57] IgM is not present in newborn secretions. Both IgG and IgA levels are increased in the secretions in the presence of infection. Neonatal infants receiving exchange transfusion with IgA-rich adult blood or those with elevated serum IgA do not have an earlier appearance of IgA in the secretions.[55,56,58]

Despite the absence of IgA in neonatal secretions, free secretory component regularly is found in the urine and saliva of newborn infants.[59] Remington and Schaefer[60] found free secretory component in the urine of newborn premature infants in the absence of urinary IgA. IgA appeared initially from 40 to 64 days in the urine.

IgD

IgD also does not cross the placenta, and is usually not detected in cord blood. When present, IgD levels are 5 to 30 percent of the normal adult level of 3 mg per 100 ml. Evans et al[29] detected IgD in seven of 84 newborns (8 percent) by a commercial immunoplate system. Berg detected IgD in only one of 64 premature newborns.[27] Maternal IgD levels tend to increase in pregnancy.[61,62]

IgE

IgE and its reaginic activity do not cross the placenta.[62-65] IgE was not detected in 29 of 34 newborns by skin testing with anti-IgE serum;[64] the skin test did become positive during the first month (mean of 21.7 days). In the same study the mean cord IgE level of 13 newborns was 39.1 ng per ml as assayed by radioimmunoassay compared to the maternal level of 177.2 ng per ml in agreement with the findings by Johannson,[66] who found a mean cord IgE level of 36.3 ng per ml compared with a maternal level of 286 ng per ml. IgE skin test reactivity may be related to defective fixation of IgE to neonatal skin. It is of interest that there was a more rapid conversion of the IgE skin test to positive in the bottle-fed than in the breast-fed infants.[64]

In a later study, Bazaral et al,[65] using a modified radioimmunoassay, found cord serum levels of IgE to be 2.1 units per ml (0.45 units IgE was approximately equal to 1 ng) with a range from less than 1 to 7.5 units per ml. The mean maternal IgE was 205.3 ng per ml. No correlation existed between maternal and infant IgE levels. The mean level of IgE at six weeks of age was 5.53 units per ml and at six months of age was 57.6 units per ml. The IgE levels of six-month-old infants from allergic families was 98.6 units per ml, compared with the mean of 29.0 units per ml among infants with a negative family allergy history. Among the six-month-old infants, the three with clinical allergic disease were among the four with the highest IgE levels.

Immunoglobulin Abnormalities Among Selected Groups of Newborns

Premature Infants

Premature infants have lower levels of IgG than do term infants as a result of diminished placental transport during gestation.[26-30] Thus the IgG level of neonatal cord blood is reduced in proportion to the degree of immaturity; small viable infants of 29 to 30 weeks gestational age weighing near 1,300 grams have mean IgG levels of 400 mg per 100 ml, 35 percent of adult and term cord blood levels.[30]

Since the IgG half-life (T½) is about 25 days at serum levels above 200 mg per 100 ml and the time of onset of IgG synthesis is not significantly altered, the physiologic hypogammaglobulinemia that ensues at age three to six months is more severe and prolonged in the premature. Approximately 50 percent of infants born before the 32nd week of gestation will have IgG levels less than 200 mg per 100 ml from the 16th to the 25th week of life. The difference between individual infants can be attributed to varying times of onset of endogenous gamma-globulin synthesis.

This exaggerated physiologic hypogammaglobulinemia may play an important but as yet undefined role in the increased susceptibility to infection noted among prematures. This is manifested by increased morbidity and mortality rates among prematures[67] and a higher incidence of sudden infant death syndrome.[68] It should be noted that two studies could not demonstrate abnormal immunoglobulin deficiencies among infants succumbing of the sudden infant death syndrome.[69,70]

The mean IgM and IgA levels of prematures are also decreased due to diminished neonatal synthesis.[26,27,29] Evans et al[29] noted that the mean IgM cord serum level of 24 term infants was 16 mg per 100 ml and that 25 percent had no detectable IgM; in contrast, the mean IgM of 21 infants of 28 to 31 weeks gestational age was 4.4 mg per 100 ml and 71 percent had no detectable IgM. The IgA level of the term newborns was 6.6 mg per 100 ml (and undetected in 71 percent) compared with 2.2 mg per 100 ml in prematures of 28 to 31 weeks (and undetected in 86 percent). Because of considerable scattering, neither IgM nor IgA levels in cord serum can be correlated with gestational age.

Yeung and Hobbs[28] and Thom et al[26] demonstrated a straight-line relationship between the gestational age and the logarithm of the cord IgG level. We noted that gestational age correlated better with the IgG level than with the log IgG level[30] (see Chart 1). There is a lesser but still significant correlation of the cord IgG level with the birth weight.[27,30]

The time of onset of IgM and IgA synthesis is the same in premature infants as in term infants,[71] and they show an equal or near-equal antibody response to injected antigens or infectious agents.[18,19] However, IgM synthesis in prematures may be somewhat less than in term infants. Berg[27] noted significantly lower IgM levels in three-weeks-old premature infants than in three-weeks-old term infants. This in part may be due to lessened exposure to infectious agents inasmuch as prematures are kept in incubators.

The therapeutic use of immune serum globulin (ISG) to prevent infection in prematures has been proposed.[72] Amer et al[73] gave alternate prematures albumin or ISG injections and noted a slightly diminished incidence and severity of infection in the ISG-treated group. In the first month of life, there were five deaths among 136 in the albumin group, and one death among 135 in the ISG group. Further studies must be completed before a definite recommendation can be made.[74]

Small-for-Dates Infants

The IgG levels of 46 of 47 small-for-dates (SFD) newborns (newborns less than two standard deviations below the expected weight for their gestational age) were studied by Papadatos et al,[75] who found that the IgG levels of SFD newborns were less than the IgG of normal newborns of equivalent gestational age, but higher than the IgG of normally-grown infants of equivalent birth weight. They suggested placental dysfunction as a cause for both the intrauterine growth retardation and lower IgG levels. Yeung and Hoggs[28] also found low levels of cord IgG in all 28 SFD infants compared with normal sized infants; 12 had levels less than two standard deviations below their expected mean. Evans et al,[29] however, found that only two of 44 SFD infants had cord IgG levels less than the tenth precentile for gestational age. Eight of the 28 SFD infants studied by Yeung and Hobbs[28] had cord IgM levels over 15 mg per ml, the upper limit of normal for their laboratory. Evans et al[29] found that eight of 44 SFD had elevated (more than 15 mg per 100 ml) IgM levels. IgA levels were not regularly detected in cord blood of SFD infants.[28] Twins, despite being SFD, have normal levels of IgG.[28]

Post-Mature Infants

Yeung and Hobbs[28] found that ten of 12 post-mature babies, two of them SFD, had lower than expected levels of IgG (mean 772 mg per 100 ml compared with control newborns of 1,100 mg per 100 ml). Ackerman et al[76] could not confirm a decreased IgG in 40 post-mature infants (the levels were actually slightly higher than in normal term infants), but they did find that ten of 40 of post-mature infants had detectable IgA. Among those with detectable IgA, the mean concentration was 28 mg per 100 ml in contrast to the trace levels or absence of IgA in term infants. A maternal-fetal bleed was excluded by demonstration of a progressive increase of IgA on serial determination. No abnormalities of IgM were noted.

Infants with Congenital Infections

Elevated IgM in Congenital Infection. Intrauterine infections, primarily but not exclusively those associated with rubella virus, cytomegalovirus, treponema pallidum and toxoplasmosis, may result in easily recognized sepsis in a neonate; in other instances, the infection may be subclinical and not manifest until months or years later.[46,77] Recognition of the condition is important in treatment, prognosis, and isolation procedures.

Stimulated by the observations of Alford[78] and Bellanti et al,[79] who observed prominent immunoelectrophoretic IgM arcs in infants with congenital rubella, Stiehm et al[44] suggested that an elevated IgM level upon quantitative IgM determination of cord serum would be an indicator of congenital infection. This was based on the fact that the infected fetus synthesizes specific IgM antibodies

TABLE 3.—*Incidence of Elevated IgM Levels in Random or Serially Collected Umbilical Cord Sera of Various Groups of Newborns*

Author, Year, Reference	*Population Studied*	*IgM Levels*	
		Number Elevated in Number Studied*	*Percent with Elevation*
Stiehm et al (1966)[44]	Random Newborns (mixed income)	7/129	5.4
Stiehm and Nichol (1968)[87]	Consecutive Newborns (middle income)	2/1100	0.2
Alford et al (1967,1969,1971)[46,77,82]	Consecutive Newborns (mixed income) (1967-1968)	123/2916	4.2
Alford et al (1967,1969,1971)[46,77,82]	Consecutive Newborns (mixed income) (1968-1969)	69/3035	2.3
Hardy et al (1969)[88]	Consecutive Newborns (mixed income)	132/2623	5.0
Sever et al (1969)[85]	Consecutive Newborns (middle income)	14/1768	0.8
Miller et al (1969)[83]	Consecutive Newborns (mixed income)	135/5006	2.7
Lechtig and Mata (1970,1971)[89,90]	Random Newborns, (mixed income from urban underdeveloped country)	1/16	6.3
Lechtig and Mata (1970,1971)[89,90]	Random Newborns, (poor income from rural underdeveloped country)	55/155	48.7
Dent et al (1971)[86]	Consecutive Newborns, (mixed income)	4/100	4.0
Gotoff et al (1971)[81]	Random Newborns, (low income)	41/1659	2.5
Gotoff et al (1971)[81]	Random Newborns, (middle income)	27/2626	1.0

*All the studies have used an IgM of 20 mg per 100 ml or above to be abnormally elevated except for Gotoff et al[81] who used 17 mg per 100 ml, and Hardy et al[88] who used 30 mg per 100 ml.

and immunoglobulins which are readily detectable in cord blood, since maternal IgM does not cross the placenta. Stiehm et al[44] initially used a cord IgM of 20 mg per 100 ml or greater (mean +2 standard deviations) to indicate an abnormally elevated level. Although other investigators have used higher or lower values, most continue to use a cut-off IgM level of 20 mg per 100 ml.[82-86]

The initial study indicated that all infants with congenital infection had elevated cord IgM levels.[44] Subsequent studies[46,77,80-86] confirm that cord IgM is increased in congenital infection but not in all infected infants. Alford[46] found that 38 of 43 infants with clinical congenital infection had pronounced elevation of IgM; however, McCracken et al[84] noted that only 12 of 88 with congenital rubella (18 percent) had elevated IgM.

The degree of elevation of the IgM level in congenital infection is dependent on several factors; in general the more affected the infant is, the more likely he is to have elevated IgM. Further, the type of congenital infection may be important; in our experience infants with rubella have higher IgM levels than other infected infants. The maturity of the infant may be important; a very small premature may have a lessened IgM response than an older infant.

Incidence of Elevated Cord IgM. Because of the simplicity and wide availability of IgM determinations, many investigators have surveyed the IgM levels of various newborn populations in a search for inapparent congenital infection. A summary of several of these studies is given in Table 3. The incidence of elevated cord IgM ranges from 0.2 to 5.4 of cord blood, varying perhaps to some extent on the year but to a major extent on the socio-economic status of the newborn population. A consistent feature is the higher mean IgM level and the higher percentage of infants with IgM elevations in low socio-economic groups. In rural, underdeveloped countries, nearly 50 percent have elevated IgM;[89,90] since the mean IgM is so high an elevated IgM is of considerably less value as an indicator of congenital infection. The increased antigenic stimulation which is occurring in newborns of low socio-economic status may also be an important factor in the increased infant morbidity and mortality in these populations.

Cord IgM Screening Procedure. Despite the above limitations, measurement of cord IgM has proved to be of value in the evaluation of infants suspected of congenital infection. Alford,[46] who has had more experience with this procedure than anyone else, has shown that the infection rate of infants with elevated IgM was much higher than in those with normal values. In his studies shown on Table 3, among the 202 infants with elevated IgM, specific infections were diagnosed in 69. Virtually all of these infants were asymptomatic at birth. Alford also found a higher incidence of central nervous system abnormalities during the follow-up period. This is contrary to the finding of Gotoff et al[81] who noted no difference in the prognosis between those with and those without elevated cord IgM levels. Alford[46] found the frequency of congenital infection was 0.56 percent among 7,500 general deliveries; in contrast the frequency of congenital infection was 20 percent among 202 infants with elevated IgM. Thus the infection rate is increased 40-fold among infants with elevated IgM levels.

An IgM determination is indicated for any infant suspected of having a congenital infection. Suspicious clinical features include petechiae, hepatosplenomegaly, skin rash, congenital heart defect, microcephaly, inguinal hernia, thrombocytopenia, jaundice and anemia. Further, if the infant is small for gestational age or does not thrive, congenital infection must be suspected. Finally, if the mother is known to have been exposed to rubella or another infectious agent or had a viral syndrome during pregnancy, her newborn infant is suspect.

To be of clinical significance an elevation of IgM must be the result of increased fetal synthesis and not due to maternal blood in the circulation. Indeed, Miller et al[83] felt that in 60 percent of 135 cases of cord IgM elevation, placental leaks were the cause. This may occur in about 1 percent of all deliveries.[91] In the presence of a maternal-fetal bleed the infant's IgA level may exceed the IgM level, reflecting the IgA:IgM ratio in maternal blood. In contrast, in congenital infections, the IgM level exceeds the IgA. For this reason both IgM and IgA levels should be measured routinely on cord blood submitted for IgM analysis.

Further, in the presence of a maternal-fetal bleed, the initially high IgM level will fall significantly in three or four days (because of the short half-life of IgM); in contrast an elevated IgM as a result of congenital infection will remain elevated or increase.

Definitive Diagnosis of Congenital Infection. Two approaches to the definite diagnosis of congenital infection are available. The first is demonstration of the organism by culture of blood, throat, stool or urine. The second is by serological means.

A single positive antibody titer in an infant is of limited significance, since it may only be a reflection of transplacental maternal antibody. Since maternal antibody falls with a half-life of 25 days, a rising or persisting antibody titer, measured on paired specimens drawn at least 30 days apart and run simultaneously, indicates endogenous antibody synthesis and congenital or neonatal infection. A finding of higher antibody titers in the infant's serum in paired maternal and infant specimens (that is, drawn simultaneously) is only significant if the infant's titer is considerably higher (greater than two dilutions) than the maternal titer, inasmuch as mature infants have higher IgG levels than their mothers as a result of active transplacental transport.[25]

A new approach, which permits the immediate diagnosis of congenital infection is the demonstration of IgM-specific antibodies in the newborn serum. Such procedures are available in several laboratories for the rapid diagnosis of congenital rubella,[92,93] syphilis,[94] toxoplasmosis,[95] and cytomegalic inclusion disease.[96] Since IgM does not cross the placenta, the presence of IgM antibodies indicates that the infant is synthesizing the antibody and is or was infected.

Two methods are used to show that the antibody is IgM. The first is to fractionate the infant serum and determine antibody titers on the isolated IgM and IgG fractions.[92] The second is to react the test serum with the antigen, and then identify the immunoglobulin class of the antibody by immunofluorescence using antiserum to human IgM or IgG.[93] These two general methods can be used for the identification of the antibody class to other organisms suspected of causing congenital infection.

Post-Natal Immunoglobulin Studies. Studies of immunoglobulin levels beyond the neonatal period in 22 infants with congenital rubella have been reported by Soothill et al.[97] The initial IgM elevation persisted throughout the first year, often increasing to levels five to ten times normal in nearly all of the 22 infants studied. Most of the IgG values were also high, with lessened physiologic hypogammaglobulinemia; however, six of the 22 infants had decidedly low levels of IgG (in the hypogammaglobulinemic range) and two had symptoms of immunodeficiency.

Infants with Post-Natal Infections

An infection acquired at or shortly after birth will serve as a stimulus for IgM synthesis.[50,98-101] However, since IgM levels normally rise rapidly after birth (probably as a result of bacterial colonization of the gastrointestinal tract), the post-natal IgM level must be significantly greater than that expected physiologically to be of clinical significance.

Blankenship et al[50] reported significantly elevated IgM levels in 27 of 31 infants with viral or bacterial infections in the first 30 days of life. The

IgM levels were measured at three to five day intervals after birth and plotted on a graph such as is shown in Chart 3. The IgM levels began to increase within five days of infection. The IgM levels were generally found to be above the first standard deviation and often above the second deviation for age (see Chart 3). An IgM level above 50 mg per 100 ml at any time in the neonatal period is cause for suspicion of systemic infection.

Panayotou et al[98] reported IgM and IgA elevations in 11 premature newborns with gastroenteritis; ten of them had IgM levels or IgA levels, or both, of 50 mg per 100 ml or greater within the first 30 days of life. The mean levels of IgA of infected newborns were significantly elevated—about twice that of non-infected controls at ages 10, 20 and 30 days. Berg[99] showed that five infants with recurrent (but not severe) infections had significantly higher mean IgM and IgA levels from age six weeks to one year than did ten infection-free infants. IgG levels were the same in both groups.

Khan et al[100] found elevated IgM levels in a significant percentage of 613 infants with various infections occurring at various periods in the first two years of life. For example 29 of 39 neonates with sepsis had IgM levels two standard deviations above the normal level for age. They felt that IgM levels were particularly useful in the diagnostic evaluation of infants suspected of sepsis and previously treated with antibiotics. Nahmias[101] reports that in neonates suspected of sepsis 90 percent are not confirmed by culture; however, in 17 such neonates in whom a significant IgM increase developed, eight had proven infections.

Cord IgM elevations have not been found in neonatal biliary atresia,[44] neonatal hepatitis,[44] mongolism,[102] and congenital malformations,[103] suggesting that congenital infection is not an etiologic factor in these conditions.

Miscellaneous Disorders

Maternal Agammaglobulinemia. Newborns born to mothers with agammaglobulinemia will have low levels of IgG in the cord blood as a result of diminished placental passage.[104,105] Normal levels of IgM and IgA are noted. There are no reports of unusual propensity to infection among such infants.

Antibody Immunodeficiency. Neonates with congenital X-linked agammaglobulinemia usually are not symptomatic until after six months of life, by which time maternal IgG levels have waned.[106] Since there may be some synthesis of IgM and IgA in the first few months, it may not be possible to diagnose this disorder in the first six months. However, a complete absence of IgM and IgA, in the presence of a continuous fall of IgG, is indicative of defective antibody synthesis. Patients with combined immunodeficiency (Swiss agammaglobulinemia) have onset of symptoms in the first three months of life due to their profound cellular immunodeficiency; their immunoglobulins may be in the normal range in this period. In congenital antibody immunodeficiencies with or without cellular immunodeficiency, functional tests of antibody synthesis are indicated.[106]

Mongolism. Miller et al[102] reported that newborns with mongolism have lower levels of cord IgG than do normal controls. Twenty-four newborn Caucasian mongols had mean cord IgG levels of 684 mg per 100 ml, significantly below the IgG level of 1,144 mg per 100 ml in 39 Caucasian control newborns. Eight Negro mongols had mean IgG levels of 931 mg per 100 ml compared with the IgG level of 1,293 mg per 100 ml among 48 Negro control newborns. These differences were highly significant and could not be attributed to prematurity, birth weight, age of collection, maternal age, sex, or other factors.

Intrauterine Transfusion. Hobbs et al[107] reported elevated cord IgM or IgA or both in ten of fourteen infants given intrauterine transfusions for hemolytic disease of the newborn. Three had cord IgM levels exceeding 20 mg per 100 ml, ten had detectable IgA, and five had IgA levels of 10 mg per 100 ml or greater. They believed that these elevations could not be attributed to the transfused blood but instead represented an immune response to the antigenic stimulation of homologous blood.

Phagocytic and Opsonic Studies in Newborns

We consider now several "non-specific" components of neonatal host defenses—phagocytes and opsonins. While the classification of "specific" and "non-specific" immune mechanisms has some utility, it is important to remember the limitations of this distinction. For example, among the opsonins, specific antibodies are highly effective. Is the role of antibody in enhancement of phagocytosis, then, to be considered "specific" or "non-specific"? Similarly, although such processes as chemotaxis and phagocytosis appear to be "non-specific" in basic nature, the role they play in the elaboration of the specific immune response is at present unclear, and may in future prove to have at least some specificity. The value of the classification is primarily to permit orderly consideration of the rapidly accumulating store of data involving individual processes of the inflammatory-immune response.

CELLULAR FACTORS

Among the cellular activities that play a role in protecting the host from infectious agents are movement, phagocytosis and post-phagocytic killing of ingested microorganisms. While each of these will now be considered separately, they are best regarded as a continuum, within which any type of defect may result in increased numbers of infections or defective response to infections.

Polymorphonuclear Leukocyte (PMN) Functions

CELL MOVEMENT

Knowledge about cell movement has increased rapidly over the past few years.[108] It is now recognized that the mechanism(s) by which neutrophils move involve a complex series of interactions between humoral and cellular components. It appears that at least two types of neutrophil movement may be involved in the mobilization of cells in inflammation.[109] The first of these is *chemotaxis,* which refers to specific, directed migration of cells toward an inflammatory focus. The second type of neutrophil movement is *random mobility,* which is characterized by nondirected or Brownian type movement of cells. Chemotaxis is generally measured by some type of modified Boyden assay,[108] the principle of which consists of separating a cell suspension from a source of chemotactically active material(s) by a small-pored filter. The number of cells which traverse the filter in a given period provides an index of chemotactic activity. The mechanisms by which cells are activated to chemotax are not completely understood. Ward and Becker have shown that two cell-bound serine esterases are required,[110] one of which exists in or on the leukocyte in an already activated state. The other is enzymatically inert and becomes activated following interaction with the complement system. Qualitative or quantitative deficiencies of either or both of these esterases might, then, result in defective cell movement.

Miller[111] compared chemotaxis of PMNs from normal human neonates with that of PMNs from normal control subjects, toward a variety of chemotactically active materials. In all cases neonatal PMNs showed significantly decreased chemotactic response. The nature of this deficiency is unknown.

Random mobility of PMNs has been studied by several methods. Current data suggest that random mobility, as measured by the capillary tube migration method, involves different mechanisms of cell movement than chemotaxis.[112] In this type of assay, standardized suspensions of PMNs are placed in micro-hematocrit tubes and placed upon a microscope stage that is then turned to the horizontal. This puts the tubes into a vertical position, as with a sedimentation rate preparation. The tubes are examined through an ocular micrometer, and the maximum distance that cells have moved upward in the tube over a given time is measured. By this method, neonatal PMNs appear to be somewhat less active in random mobility than PMNs from older children and adults.[109] The potential clinical significance of this and other functions of PMNs in the neonatal inflammatory response is considered below.

PHAGOCYTOSIS

The ability of PMNs to ingest, or phagocytize, micro-organisms is a major step in the inflammatory process. The classic studies of Metchnikoff first emphasized the importance of the PMN or "microphage" in body defenses.[113] It was soon suggested, however, that humoral factor(s) played at least an equal role in the phagocytic process.[114] In 1904, the term, *opsonin,* or "purveyor of dainties," was coined.[114] We now recognize that both humoral and cellular factors are of significance in the phagocytic process, and that deficiencies of either can result in clinically significant dysfunction. We consider here the cellular events of phagocytosis, with special reference to the neonate.

Surprisingly few studies of phagocytosis in neonates were performed until the beginning of the last decade. Of those that were, the majority demonstrated a relative deficiency of phagocytic activity in whole blood of newborns as compared with that of older children and adults.[115-120] The studies varied considerably in such factors as the challenge particle used in the assay, the serum concentration, the source of the cells, and a variety of other experimental conditions. The major problem, however, was that the use of whole blood in the assays made it impossible to evaluate the separate effects of humoral and cellular components.

Data are now available on the individual humoral and cellular aspects of the neonatal phagocytic process. In one group of studies, the phagocytic activity of isolated neonatal leukocytes has been found to be normal.[121-125] Within this group, however, the leukocytes and challenge particles (E. coli, S. aureus 502A, S. marcescens, Strep. pyogenes, D. pneumonia and P. aeruginosa) were incubated in the presence of serum concentrations of 10 percent or more. In *lower* concentrations of serum, however, PMNs from neonates may be less phagocytic.[117] Matoth, in 1952, demonstrated that phagocytosis of starch granules by leukocytes from adults and from cord blood of term neonates was equal in the presence of final concentrations of maternal serum in excess of 10 percent. In the presence of lower concentrations of maternal sera, however, cord blood PMNs were less efficient in phagocytosis than adult PMNs. More recently, the phagocytosis by PMNs from neonates and normal adults of washed, baker's yeast particles has been compared in the presence of varying concentrations of plasma.[126] In final concentrations of 2.5 percent plasma or less, neonatal PMNs ingested far fewer yeast particles than those from adults.

It appears therefore that under certain experimental conditions, neonatal PMNs are deficient in phagocytic activity. Possible *in vivo* support for this observation comes from the data of Forman and Stiehm,[121] who found that PMNs from six of nine term infants with various underlying clinical disorders were sufficient in phagocytosis.

In premature infants, the data are not as clear. Of the few studies which have been performed on this question, the variations of particles and experimental conditions make an overall summary difficult. Miyamoto, using whole blood and killed streptococci,[127] found PMNs from prematures were less phagocytic than those from term infants during the first week of life. These studies, however, did not distinguish between humoral and cellular components of the phagocytic process. Gluck and Silverman[128] found that PMNs of premature infants ingested normal amounts of India ink particles in the presence of adult serum, but diminished numbers in the presence of serum from prematures. Cocchi and Marianelli[129] observed normal phagocytic activity toward viable Pseudomonas aeruginosa in PMNs from premature infants. PMNs from 13 of 14 premature infants studied by Forman and Stiehm[121] phagocytized normal numbers of S. aureus 502A and S. marcescens. Phagocytic activity of PMNs from premature infants in the presence of serum concentrations less than 10 percent has not been studied.

BACTERICIDAL ACTIVITIES

Clinical interest in cellular killing of ingested microorganisms was heightened following the description of Holmes and coworkers of an inborn error of neutrophil function resulting in decreased bactericidal activity of PMNs from patients with chronic granulomatous disease (CGD).[130] There have been a number of investigatons of bactericidal activities of neonatal PMNs, but there are major inconsistencies in these studies, and little consensus information has yet emerged. In studying the fate of viable Pseudomonas aeruginosa within PMNs of premature infants, Cocchi and Marianelli[129] found that bactericidal rates in premature leukocytes were equal to those in controls at 90 minutes, but by three hours were decreased. These differences were unaffected by serum concentrations. Bactericidal activities of PMNs from nine of 25 full-term infants studied by Coen and coworkers were decreased within the first 12 hours of life.[122]

A number of investigators have demonstrated normal bactericidal activities in neonatal leukocytes.[120,125,131] Organisms used in these studies included S. aureus 502A, E. coli, and Pseudomonas aeruginosa. The many inconsistencies and differences in method make it difficult to summarize what has been learned. It appears, however, that the neonatal leukocyte is relatively normal in bactericidal activity.

METABOLIC ACTIVITIES

Interest in the functional activities of PMNs in the neonatal inflammatory process has been accompanied, naturally, by inquiries into the metabolic status of these cells. The problems to which we alluded in the previous section are all the more apparent when one attempts to perform sophisticated metabolic measurements of PMNs. Such variables as pH, temperature, and state of cell, whether resting or phagocytic, are important to the interpretation of results.

In studies on actively phagocytizing PMNs, both Donnell and coworkers[132] and Coen and coworkers[122] found that PMNs from term infants showed less increase of hexose monophosphate shunt

(HMP) pathway following phagocytosis than that seen in adult PMNS.

Park and coworkers[131] found that neonatal PMNS in the resting phase consumed twice as much oxygen as matched maternal PMNS. Following phagocytosis, however, neonatal and maternal PMNS showed similar increases in oxygen consumption and glucose utilization.

Post-phagocytic reduction of nitroblue tetrazolium (NBT) dye to blue formazan has been compared between neonatal and adult PMNS, with conflicting results. Park and coworkers found increased reduction of NBT within neonatal PMNS,[131] while Bellanti and coworkers noted decreased reduction of NBT.[133] McCracken and Eichenwald[125] found normal reduction of NBT within PMNS from 41 infants varying in age from two hours to 71 days.

Rather than attempt to establish one of these studies as being correct to the exclusion of the others, it should be recognized that the differences are probably explained by variation in the conditions of the assays, particularly the time of sampling of the NBT dye reduction. Bellanti and coworkers suggested that activity of PMN glucose-6-phosphate dehydrogenase (G6PD) decays at a significantly greater rate in neonatal than in adult PMNS.[134] They also found a decrease of G6PD and NBT reduction during the first six months of life, followed by a continued increase with age.

Other Cell Types

Little is known of the relative functions in neonates of other cells of the inflammatory response. In the specific immune response, lymphocyte function in neonates is probably normal. As for elaboration of inflammatory mediators, or "lymphokines," little is known of the relative function of neonatal PMNS.

The function of the neonatal eosinophil may be decreased, as suggested by data obtained by the inflammatory cycle technique of Rebuck and Crowley.[135] In this procedure an area of skin is abraded with a sterile scalpel blade, and a cover-slip is placed over the inflammatory site. The cover-slip is changed periodically, replaced with a new slip and is stained and examined microscopically. In a normal adult "skin window" response, PMNS predominate over the first four to twelve hours, followed by a shift to a largely mononuclear cell response.

In studies of the inflammatory response in term neonates, Eitzman and Smith[136] found increased numbers of eosinophils in the second-hour and fourth-hour exudates of newborns over, but not under, 24 hours of age. By contrast, however, Bullock and coworkers[137] were unable to find such a consistent abnormality. In their study, only 13 of 61 babies studied showed significant skin window eosinophilia. They suggested that the group with abnormal eosinophilia represented a subgroup with a possible allergic diathesis. This hypothesis is as yet untested.

Skin Reactivity and Inflammatory Response

Since the interpretation of many of the assays of inflammatory-immune function depends upon the reading of some form of skin response, it should be borne in mind that an abnormal cutaneous response may reflect a basic abnormality of skin reactivity rather than a primary defect of inflammatory or immune nature. An example of errors that may occur unless this warning is heeded is the conclusion that deficient skin test responses in neonates are due to defective cell mediated immunity.

It has long been observed that neonates show poor localization and inflammatory response to dermal infections. This is due in part to certain of the deficiencies of the neonatal inflammatory response (see below), but is probably due also to the fact that neonatal skin is relatively deficient in the manifestation of inflammation. In experimental studies, Seto and Drachman observed the response to dermal infection in weanling and adult rats.[138] Upon dermal injection of pneumococci, the weanling rats had (1) increased incidence of bacteremia and death, (2) delayed migration of neutrophils, (3) delayed migration of mononuclear cells, and (4) poor localization and increased spreading of bacteria.

Eitzman and Smith[136] found that the skin of newborns responded poorly to irritation and failed to localize inflammation when compared with the skin of older children.

Studies of cutaneous inflammation in neonates (by the previously mentioned Rebuck "skin window" method) demonstrated a relatively delayed and less intense shift from the predominately polymorphonuclear to mononuclear phase than in adults.[136,137,139]

Whether the above studies are the result of intrinsic abnormalities in neonatal skin or they simply mirror the observed deficiencies of the inflammatory response is not clear. For example, poor response to irritation and failure to localize cutaneous infection could result from deficient chemotaxis and phagocytosis. At present the correlations which can be drawn between *in vitro* abnormalities of leukocyte function and clinical significance are limited.[108,109,111] The future should see great interest in definition of these relationships and lead to increased knowledge of the roles these deficiencies play in enhanced susceptibility to infections in the neonate.

HUMORAL FACTORS

As has been discussed, it is difficult to adhere closely to a precise classification of the components of the inflammatory-immune response. This is as true with the humoral components as it was with the cellular components. Immunoglobulins, for example, which have been considered in depth as mediators of the "specific" immune response are also among the most potent activators of the complement system, a presumptively "non-specific" mediator of inflammation.

Complement

Appreciation of the wide range of biologic activities mediated by the serum complement system has increased greatly over the past decade. While specific application of this information to the neonate is at a preliminary stage, the field promises to yield applicable information in the not too distant future.

No attempt will be made here to comprehensively review the serum complement system. The reader is referred to several excellent recent reviews.[140,141] In brief, the complement system consists of 11 identified proteins. Upon activation by an appropriate stimulus, such as an antigen-antibody reaction, the activated first component of the reaction, or C1, is formed. C1, as well as subsequently reacting components in the sequence, has enzymatic activity and interacts with the next component in the sequence. At completion, all components have reacted in sequence—C1,4,2,3,5,6,7,8,9. There are three basic types of biologic activities which are mediated by the complement system:

1. Cytotoxic reactions occur as a result of interaction of all components upon a particular cell surface or membrane. In the classical model of sheep cell hemolysis, for example, the end result of complement reaction upon the sensitized sheep erythrocyte membrane is damage to the membrane, the result of which is an osmotic lysis secondary to the hole which has been "punched" in the membrane.[140] Complement reaction can damage virtually any type of cell, lysis being but one example of such an effect.

2. A second type of complement mediated biologic activity involves changes which occur upon the membrane involved in the complement reaction, as the individual components react in sequence. For example, a pneumococcus which has reacted with antibody and has activated the complement sequence becomes far more readily phagocytized once the first four components have reacted. In other words, total reaction of the system may result in cytotoxic effects, but partial interaction may alter the entire antigen-antibody complex in such a way that phenomena such as opsonization and immune adherence take place. Although the actual mechanisms by which these intermediate steps alter biologic activity is unknown, and may actually prove to be the same as that of the cytotoxic effects of complete reaction, a separate set of biologically significant activities is involved.

3. The third, and potentially most significant mechanism for mediation of biologic activities of the complement system, pertains to low molecular weight "split products" of the native components which are released into the circulation upon activation of the parent molecule. Such materials possess potent activities as histamine releasers (anaphylatoxins) and in the attraction of leukocytes (chemotactic factors). The elaboration of such biologically active materials into the circulation has obvious potential in a wide range of clinical disorders of the inflammatory response.

It now appears that at least two distinct pathways exist by which complement mediated activities can be triggered. The first of these, or the classic pathway, involves, most commonly, activation by an antigen-antibody complex. In the so-called "alternate pathway," however, the initial components of the system are by-passed, and activation takes place directly through the C3 molecule. Among the agents which activate the alternate pathway are zymosan, inulin and endotoxins.

The measurement of complement has provided a number of pitfalls. For many years, it was felt that adequate assessment of complement could be done by measuring total hemolytic activities and immunochemical determinations of C3, or so-called $\beta 1\text{C}/\beta 1\text{A}$. It is now clear, however, that such measurements may not provide an adequate estimate of functional activity of a particular component. Further, even specific quantitative deficiencies of individual components may not reflect functional status of all activities mediated by that particular component.[142] This means that studies of complement components by immunochemical or hemolytic measures may not adequately reflect biologic activities in newborns.

Synthetic studies have revealed synthesis of the third component (C3) in fetal tissues by immunochemical techniques as early as five and a half weeks of gestation.[1,143] Fireman and coworkers found C3,C4 and C5 levels were decreased in term infants and prematures as compared with maternal and normal adult levels.[144] Propp and Alter found the mean cord levels of C1q,C3,C4 and C5 in sera of term neonates to be 0.752,0.562,0.550, and 0.602 of the respective maternal concentrations.[145] Koch and coworkers found relatively low levels of the first four components in cord blood, as compared with levels in blood from normal adults.[146]

Total hemolytic complement activity in newborns is approximately half of that in matched mothers.[119,144,147-150]

Functional Activities

OPSONIC ACTIVITIES IN PREMATURES AND NEWBORNS

The importance of separate evaluation of humoral and cellular components of the phagocytic process has been emphasized in the preceding section. Complement-derived materials are among the important opsonins in plasma. Measurements of opsonic activity in neonatal plasma have generally revealed a deficiency when compared with that of older children or adults.

As previously noted, the concentration of serum or other source of opsonin may affect the results obtained in a given assay. Miller compared the opsonic activity of neonatal and normal adult plasmas toward baker's yeast particles.[126] Plasma from the neonates had less opsonizing activity toward yeast particles than that from the adult group. The difference was statistically significant, however, at final plasma concentrations only of 10 percent or below.

Opsonic activity of neonatal sera toward various bacteria has been studied by a number of investigators. Dossett and coworkers found neonatal sera were deficient in opsonic activity toward E. coli and serratia marcescens when compared with maternal sera.[124] No difference was found between the opsonic activity of the two groups toward staphylococcus aureus or group B streptococcus. By contrast, Forman and Stiehm found no deficiency of opsonization of neonatal sera of S. aureus 502A or the same strain of serratia marcescens used by Dossett and coworkers.[121] In low birth weight infants (less than 1,925 grams), however, they found deficient opsonization toward both organisms. McCracken and Eichenwald studied opsonic activity of neonatal sera toward S. aureus 502A, E. coli and P. aeruginosa.[125] At serum concentrations of 10 to 25 percent, opsonic activity against all three organisms was diminished in infants under 3,000 grams. The greatest deficiencies were observed against the Gram-negative bacteria.

CHARACTERIZATION OF THE OPSONIC DEFICIENCY

The availability of new data on the process of opsonization has made it necessary to re-think some of our earlier concepts on the process in neonatal sera. For many years, the major thrust of inquiries into the problem centered about the role of antibodies. It was recognized that the major susceptibility to infections in neonates involved Gram-negative bacteria. As we have discussed, it has long been recognized that little, if any, macroglobulin (IgM) is transferred to the fetus. In 1963, Michael and Rosen demonstrated specific antibody to Gram-negative microorganisms in human macroglobulin.[151] Further, they showed that IgM antibodies were a thousand-fold more efficient than IgG antibodies in opsonic and bactericidal activities against Gram-negative organisms in mice.

Gitlin and coworkers showed that bactericidal activities against certain strains of E. coli and Salmonella typhosa 0901 were poorly transferred across the placenta, even when maternal titers were adequate.[21] Bactericidal activity against E. coli was found in only 40 percent of the infants, and against Salmonella in only 20 percent. When bactericidal activity in cord sera was present against either of these organisms, it was found exclusively within the IgG class.

From these studies it was hypothesized that an important factor in the susceptibility of neonates to Gram-negative infections was the deficient placental transfer of IgM antibodies.[21]

It now appears that deficiency of IgM antibodies provides only a partial explanation for the opsonic deficiency in neonatal sera. In the yeast phagocytosis system, it was found that addition of purified IgM to neonatal sera caused little, if any, increase in opsonic activity.[126] Dossett and coworkers found that complement or other heat-labile factors were necessary to amplify the opsonic potential of both IgG and IgM.[124] The enhancing effect, however, was considerably greater with IgM than with IgG, thus leading them to conclude that IgM antibodies are significant opsonins for E. coli, but that complement is necessary to demonsrate full activity.

As was discussed previously, measurements of individual complement components may not reflect functional deficiencies within the system. Thus, McCracken and Eichenwald found a relationship between C3 levels and opsonic activity against S. aureus and Pseudomonas aeruginosa in their studies, but were unable to demonstrate a similar relationship toward E. coli.[125]

There are few functional studies of complement activities in neonatal sera. In yeast phagocytosis, Miller demonstrated a functional deficiency of the fifth component of complement in neonatal sera:[152] (1) Neonatal sera, which were opsonically deficient toward yeast particles, were restored to normal by the addition of sera from strains of mice with normal amounts of C5 (B10D2 new line), but not by addition of sera from strains of mice deficient in C5 (B10D2 old line). (2) With the use of highly purified human C3 and C5, reconstitution of yeast opsonic activity occurred only when C5 was added (3) Addition of three to five-day-old stored, citrated plasma to neonatal sera was ineffective in reconstitution, while fresh plasma was entirely restorative. The reconstituting effect of five-day-old plasma was *completely* corrected by the addition of C5-containing mouse serum, or by human purified C5, but not by mouse serum deficient in C5.

Little is known of the function of the alternate pathway of complement in neonates. It seems possible, however, that a developmental immaturity of the alternate pathway may play a role in the opsonic deficiency of neonates. Koch and coworkers found low levels of properdin in cord blood as compared with the levels in adult blood.[40]

A provocative, yet unexplained observation is that of Forman and Stiehm, who found that in low birth weight (less than 1,925 grams) infants, decreased levels of IgG appeared responsible for the opsonic defect.[121] In preliminary data, they found that the opsonic defect in six of these infants against their test organism could be corrected *in vivo* by intramuscular injection of Cohn fraction II (largely IgG globulin) or *in vitro* by the addition of IgG as opsonin.

THERAPEUTIC APPLICATIONS

One of the obvious gains to be anticipated from more complete characterization of the opsonic deficiencies of neonatal plasma is improved therapy in neonatal septicemia. While there is as yet insufficient information to establish a recommended therapeutic approach, there are clear trends emerging.

In order to summarize these trends, one must first attempt to reconcile the apparent differences among the various data on neonatal opsonins. The differences in relative opsonic deficiency toward Gram-negative bacteria found by Dossett and coworkers,[124] Forman and Stiehm[121] and McCracken and Eichenwald[125] are probably explicable on the basis of varying sensitivity of assays. The summary of the three studies is that neonatal sera have significant opsonic deficiency toward Gram-negative organisms, and somewhat lesser deficiency toward S. aureus.

The data of Dossett and coworkers showed that the deficiency of neonatal sera involves at least IgM and complement.[124] They therefore suggested the use of fresh plasma infusions in the treatment of neonatal septicemia. In the yeast phagocytic system, Miller demonstrated a relative deficiency of complement, more specifically of C5 in neonatal sera.[152] The defect was corrected *in vitro* by the addition of fresh (less than 24 hours old) citrated plasma, but not by aged plasma. The significance of these data depends upon the correlation between phagocytosis of yeast *in vitro* and phagocytosis of bacteria *in vivo*. Some suggestion that they may be related comes from the similar spectrum of pathogenic agents found in neonatal septicemia and in patients with C5 dysfunction.[142] There are, thus, data from several laboratories which support the use of fresh plasma in the treatment of neonatal septicemia.

Davis and coworkers found that transfusion of adult blood to premature infants (1,000 to 2,000 grams) brought about an increase in opsonic activity of their serum for E. coli.[153] Although the data are encouraging, controlled studies are necessary before justifying the routine use of fresh plasma in the treatment of neonatal septicemia.

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Important Advances in Clinical Medicine

Epitomes of Progress—Plastic Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Plastic Surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Plastic Surgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Plastic Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, CA 94102

Plastic Operation on the Abdomen

ABDOMINAL LIPECTOMY, or panniculectomy as it has been commonly called, has been performed for many years. This operation is usually indicated for those who have lost large amounts of weight, leaving them with an abdominal apron which can be excised.

Recently, there has been a widening demand for recontouring of the abdomen. It has been described as the "bikini operation," since the scars are hidden in the bikini area. Most of the patients are attractive women who have had one or more children. Their average age is 35 years. Their problems include stria gravadium (stretch marks), a wrinkling of the skin around the umbilicus, diastasis recti and a fullness of the lower abdomen —all the results of pregnancy—as well as surgical scar deformities.

The basic steps in the operative procedure are: (1) a low transverse abdominal incision just at the level of the pubic hair line, extending laterally and below the iliac crest, (2) elevation of the entire abdominal skin and subcutaneous tissue up to the xyphoid and costal margin, leaving the umbilicus in place, (3) correction of diastasis by multiple figure 8 sutures from the xyphoid to pubis, which narrows the waist line, and (4) pulling the flap down and resecting the excess—usually four to six inches or approximately 450 grams. The umbilicus is brought up through a new incision in the abdominal skin.

Occasionally the abdominal operation is combined with other procedures such as breast augmentation, hysterectomy, or dilatation and curettage. This procedure is not exclusively for women.

FREDERICK M. GRAZER, MD

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Reduction Mammaplasty

Surgical reduction of the hypertrophic breast, although overshadowed by the more common and highly publicized operations for breast enlargement, has presented a technical and artistic challenge to the plastic surgeon for over a century. The lay public in general and a surprising number of physicians are still unaware that such an operation exists.

The indications for the operation are basically not cosmetic but rather more related to the relief of symptoms associated with excessive weight and bulkiness. As with any procedure affecting breast contour, however, cosmetic factors cannot be ignored. Progress has been slow and cosmetic results often poor due to the surgeon's preoccupation with problems of avascular necrosis. Before 1930, cumbersome multistaged procedures and free nipple grafting were resorted to out of respect for the high incidence of nipple necrosis which accompanied the dissection. An appreciation of the vascular supply of the nipple thereafter allowed single-stage nipple transposition operations with reasonable safety so long as extensive degrees of glandular resection were not needed.

In 1960, Strombeck introduced the principle of the dermis bridge which protected the nipple and virtually eliminated the complication of avascular necrosis even in the face of massive degrees of resection.

A new operation utilizing this same principle has recently been introduced which preserves the same safety features but allows greater freedom of pattern design so that the surgeon can now concentrate more fully upon the fine points affecting contour and offer the patient a more acceptable cosmetic result.

The breast is reduced to a bipedicled flap extending vertically from the inframammary fold to the new site to which the nipple is to be elevated. The flap is denuded of its epidermis to allow its burying and bears the nipple in its center. A brassiere-type pattern is preserved on either side. Most of the remaining breast tissue is resected and the new breast is constructed by folding the bipedicled, nipple-bearing flap upward and draping the brassiere skin flaps around the bulk.

Paul K. McKissock, MD

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Repair of Cleft Palate with an Island Flap

Reconstruction of a competent velopharyngeal sphincter mechanism is necessary if a person born with a cleft palate is to achieve natural and intelligible speech. The surgical management of this problem must incorporate two important features:

1. Restoration of the usual anatomical relationship with the palatal levator and tensor across the midline, fusing with the same muscle on the other side.
2. Creation of a palate of sufficient length to achieve contact with the superior pharyngeal constrictor, thereby effectively closing the oropharynx from the nasopharynx.

Recently a neurovascular island flap derived from palatal mucoperiosteum and based on the greater palatine vessels has been utilized for achievement of adequate permanent palatal lengthening. This island of oral mucosa is interpolated into a diamond-shaped defect on the nasal side of the palate that is created during the "pushback" procedure when nasal mucosa and abnormally inserted palatal muscles are divided from the posterior border of the hard palate. Inserting this tissue into the raw area on the nasal palatal surface prevents the contracture which would otherwise naturally occur during healing. This technique successfully provides a greater degree of palatal lengthening in most cases.

Libby F. Wilson, MD

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Atrophy Following Cortisone Injection for Hypertrophic Scar

Unsightly hypertrophic and keloid scars resulting from trauma, infection, or surgical procedures have presented a difficult therapeutic challenge. Simple surgical excision frequently results in recurrence of the undesirable scar. The use of x-ray therapy has improved the chance for a favorable result but disappointing scars are still quite frequent. In the past 20 years, intralesional injections of various steroid preparations have greatly improved the success rates and have in many instances rendered surgical excision unnecessary.

Two undesirable side effects of intralesional steroid injections have been encountered: cutaneous and subcutaneous atrophy and hypopigmentation of the skin at the site surrounding the injection. These effects can be minimized by using low concentrations of the injected agent—5 mg per ml triamcinolone acetonide—and avoiding injection into normal tissues surrounding the lesion. If atrophy or hypopigmentation do occur, they can be expected to resolve spontaneously in the great majority of cases simply with the passage of time (usually one to two years). The advantage of intralesional steroid therapy in treating hypertrophic and keloid scars will usually outweigh these potential disadvantages, but the patient should be informed of the possibility.

FRANKLIN L. ASHLEY, MD

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Maxillo-Facial Injuries Following Accident

WITH THE TREMENDOUS USE the American people make of the automobile there are a large number of maxillo-facial injuries, most of them promptly and adequately treated. Even so, a significant number of patients are seen months after an accident with complications. These can be any of the following:

1. Malocclusion
2. Diplopia
3. Esthetic considerations
    a. asymmetry of face
    b. flatness of cheek
    c. inequality of orbits
    d. nasal irregularity
4. Numbness of cheek and nose
5. Lack of feeling in teeth
6. Pain due to pressure on sensory nerves
7. Inadequate excursion of the mandible
8. Chronic sinusitis due to poor drainage of sinuses
9. Obstruction to breathing
10. Facial paralysis
11. Naso-lacrimal duct obstruction
12. Growth deformities
13. Temporomandibular joint dysfunction

This range of complications underscores that the degree of tolerance to mal-reduction, mal-union, and mal-position is less in maxillo-facial fractures than in fractures generally.

In some instances, these complications can be corrected fully or partially. In other cases, the injury is such that the golden opportunity was lost at the time of the original treatment. Treatment of these complications usually requires re-creation of the original fractures. The presence of motor and sensory nerves, muscles of expression and mastication, teeth, and large vessels, calls for a finesse and preciseness of technique not required in re-creating fractures in other bones. The presence of scar tissue and distortion of structures by the original injury are further complicating factors. Therefore, it is of paramount importance that these complications be avoided if possible by prompt and adequate treatment of the original injury. The same basic principles apply to maxillo-facial fractures that apply to other fractures—reduction, fixation, and immobilization.

N. JOHN WILDE, MD

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Early Orthopedic Positioning and Bone Grafting in Treatment of Cleft Lip and Palate

PROBABLY THE MOST controversial procedures in cleft lip and palate repair today are early orthopedic positioning of the maxillary segments and bone grafting of the defects. The history of both procedures is somewhat parallel. The use of orthopedic positioning measures in the early care of cleft palate patients was first described by McNeil of England in 1950. He initially described the use of a prosthetic device in an attempt to obtain some spontaneous closure of the cleft on the assumption that apposition of bone occurred with stimulation of the cleft edges. There was also the desire to move the arch segments forward, particularly the smaller one, to obtain some closure of the anterior portion of the cleft. It was appreciated that the muscle tension against the prosthetic bridge, produced by chewing and sucking motions, did move the segments. The intention was to direct the movement to shift the segments into more desirable positions.

Bone grafting of the cleft defect was discussed first in Europe around 1956. Interest in the procedures grew throughout Europe and they were first described in the literature of this country in the late 1950's. The routine for the procedures has been changed in various aspects. Initially, the prosthetic bridge was used in all clefts, unilateral and bilateral. It was placed in the infant's mouth the first few days after birth. At present it is used only for patients with a collapse of segments, and as a rule the device contains expander units. External pressure with elastic bands is used in cases of bilateral defect with protruding maxilla and in the occasional case of unilateral cleft with a jutting segment. The cleft lip is repaired when the desired alignment has been obtained, usually at about six to eight weeks of age, and the prosthetic device is then altered to accommodate the repaired lip. Bone grafts were done in all cases initially, usually at eight to ten months of age, along with closure of the anterior palate. At present, the bone grafts are reserved for unilateral clefts with defects sufficiently large that the cleft ends of the segments do not approximate following repair of the lip and in other cases. The grafts give needed support to the alar above the cleft, and also stabilize the premaxilla in the bilateral clefts after proper alignment. Nowadays the rib bone graft is used exclusively as a source of bone by most surgeons.

There has been criticism of the procedures based on statistical evidence that some configurations are inevitable and that in most clefts malalignment does not develop if not disturbed surgically. These conclusions are not considered correct by others, however, who are of the opinion that malalignment is present in some infants at birth and develops in others after repair of the lip. Proponents say that the procedures do not significantly increase the danger to the infant and they contend that leaving a cleft unrepaired through childhood or indefinitely to observe development is unacceptable. The bone grafts have been shown to survive as restructured bone tissue and good tooth buds are not necessarily injured although in some cases they do migrate into and erupt through the graft.

Interest in the procedures, as well as criticism of them, has stimulated the formation of an international group which has held three symposiums to discuss them and attempt to establish standards of technique and evaluation. The group met last in Chicago in April of 1969. The group recommended studies to establish valuable statistics on the procedures—serial photographs and dental impressions, cephalometric measurements, and x-ray studies of the arches and dentition. The procedures have persisted in spite of serious criticism for approximately 20 years, and there seems no doubt that the final word is not yet in.

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EDITORIAL

Neonatal Susceptibility to Infection

Search for an explanation for neonatal susceptibility to infection has long vexed and frustrated immunologists. Wonder and awe should be roused instead that everything works as well as it does. Prenatal maturation of immunologic function cannot be unleashed lest the fetus lose its status as a privileged allograft. Surrounded by a sea of maternal antigen, the fetus, in his sterile kingdom, remains unresponsive to the challenge. Yet the immunological apparatus must be geared to cope with the dramatic change in environmental conditions at the birth event—the transit from sterile seclusion into the microbe-ridden world. The ontogeny of the immune system is so timed that it is, in fact, set to cope at once with the extrauterine challenge, even in the prematurely born, and the newborn infant quickly manifests his immunologic competence as he encounters the various microbes of the environment. Rarely do things go wrong with this carefully constructed schedule, and overwhelming infection results from such untoward factors as premature rupture of the membranes or herpes virus in the maternal genital tract. It is, however, a small price to pay for the successful symbiotic relationship of pregnancy.

For decades, a minute and obsessive comparison of antibody titers in maternal and cord blood to a vast array of antigens has resulted in a compilation of data that may be quite unimportant, even useless and tangential to the pertinent and vital questions—this because the passive protection of the newborn infant by maternal antibody, though often regarded as essential, may be a gratuitous consequence of pregnancy in the overdeveloped society. This passive protection may have real importance in the malarious parts of the world. But several offspring of agammaglobulinemic mothers in this country have not been noted to sustain any abnormal susceptibility to infection during the neonatal period.

In this issue of California Medicine, Miller and Stiehm give a comprehensive and splendid review of what is known of the newborn and his immunity. Of necessity, they concentrate on the humoral aspects of immunity—immunoglobulin levels, antibody titers, opsonization, and phagocytic function—because these are the factors which have been most accessible to laboratory investigation. They pay little attention to cellular immunity in the newborn because little is known about it. Yet it may be of overriding importance.

If we search elsewhere for models of susceptibility to infection analogous to what is encountered in the newborn, we readily find a similar situation in patients whose cellular immunity is absent or compromised. Cellular immunity is mediated by thymus-dependent lymphocytes or T cells. Patients with poor or absent T cell function because of Hodgkin's disease, congenital thymic aplasia, immunosuppressive therapy, and so on, exhibit extraordinary susceptibility to opportunistic infections with ordinarily innocuous organisms such as the coliform enterobacilli, monilia, the herpes-pox viruses including cytomegalovirus, and Pneumocystis carinii. Such is also the cast of microbes which plague the newborn, and one is tempted by analogy to seek an explanation for the newborn's immunologic inadequacy in his poor T cell function. The newborn infant has a normal or even elevated number of T lymphocytes, but they are virginal, pristine cells and they only slowly become committed to various environmental antigens upon contact with them. Unlike the older child or adult who has become sensitized to the herpes virus or tubercle bacillus and can thus contain the infection, the newborn has inexperienced T cells that do not function to limit the spread of these microorganisms. By comparison with our extensive knowledge of humoral immunity, little is known of precisely how cellular immunity works. Further study of this most important aspect of immunity may clarify the mysteries of T cell function. Ultimately it will enable us to manipulate intelligently the cellular immunity of the newborn in trouble. The goal is the prevention or amelioration of coliform sepsis, generalized herpes or cytomegalovirus infection, and other situations where the defense mechanisms of cellular immunity are called upon.

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Fact, or Fancy?

Changing Medical Complications of Illicit Drug Use

THERE HAS BEEN an apparent increase in the incidence and nature of the medical complications of illicit drug use. Is this apparent increase a valid change in the natural history of the drug abusing patient or is it an artefact of reporting? Some communities have reported an increased incidence of death from narcotic overdose and many recent "heroin epidemics" have been related to social ills within communities. Unfortunately, careful documentation for this apparent changing incidence and nature of the problems of drug abuse are not currently available. The central difficulty in making these distinctions lies in interpreting and evaluating the medical literature about the "heroin addict." In a sense the term "heroin addict" is a misnomer since the material he abuses has been shown to contain variable quantities of many different active drugs and many potentially toxic adulterants. The situation is further complicated by the fact that those individuals with drug abuse behavior do not limit their use of drugs to one chemical class. A recent special communication[1] has noted that the hepatic dysfunction in heroin users studied by careful history and liver biopsy indicated that alcohol played a very large part in the hepatic disease noted in heroin addicts. When careful toxicological evaluations are done, especially by newer methods involving gas-liquid chromatography-mass spectrometry, it is noted that many heroin addicts are utilizing many different sedative hypnotic and tranquilizing medications. Thus it is possible that the changing medical complications are related to changes in the type of poly-drug abuse.

Another possibility to explain the apparent changing medical complications of illicit drug use is greater medical publication and awareness of the disorders likely to be present in drug abusing individuals. The common medical disorders in drug addicts have been recently reviewed.[2] These seem to be well recognized by many physicians—hepatitis, superficial skin infection, venereal diseases, extremity problems including cellulitis and gangrene due to the injection of the foreign material, and finally the most feared complication, overdose. With increased publication and medical awareness some relatively unusual and fortunately uncommon medical complications have been noted with increasing frequency. Bacterial endocarditis secondary to enteric Gram-negative infections and fungal organisms, tetanus, malaria and pulmonary edema are now widely recognized as critical medical complications. In this issue of CALIFORNIA MEDICINE there are two articles and a case report that present some of the more subtle medical complications which are now being recognized in heroin addicts. It is to be re-emphasized that the patients discussed in these articles are likely to have been abusing other drugs in addition to heroin and that the material injected which was thought to be an active narcotic could have been adulterated with other potentially hazardous materials. In addition to the pyogenic vertebral osteomyelitis, rhabdomolysis and false positive FTA-ABS, several other interesting subtle medical complications have also recently been reported. These include peripheral reactive lymphadenitis and lymphocytosis, foreign body granulomas of the lung leading to abnormal lung function, endophthalmitis, transverse myelitis, nephrotic syndrome, a polyarteritis nodosa-like vasculitis, and even chromosomal aneuploidy. Again it is not clear whether these complications represent a specific pharmacological toxicity or a complication of adulterant or merely a residual of the parenteral administration of any illicit foreign material. It should be recognized, however, that there is no definite proof that chronic administration of narcotic drugs for many years leads to any long-term medical sequelae.

Because of increasing awareness by the medical community of problems associated with illicit drug use, many physicians with limited experience and knowledge of the problems with narcotic users are now caring for patients with these difficulties. It should be noted that medical awareness must extend to some selective problems that may arise with these patients. The intravenous lines which are kindly supplied by physicians may become the ready access points for illicit drug use in the hospital. Hypotension, bradycardia and small pupils occurring even in the hospital setting should be recognized as a narcotic overdose, and the narcotic antagonist of choice—naloxone (Narcan®)

—should be available on all medical and surgical wards. It is unlikely that a patient's drug-seeking behavior will end while he is in the hospital; urine specimens should be screened frequently for drug taking in the hospital settings, visitors should be scrutinized lest they bring other drugs to the patient. If narcotics and other drugs have been withdrawn gradually during the hospital stay, the patient will have little tolerance upon hospital discharge and may return to his drug abuse behavior. The dose of the drug he takes, then, may well be far in excess of his newly lowered tolerance, and overdose may result. The management of the withdrawal syndrome from narcotics or other drugs may not appear to be controlled with the usual medications. This may indicate that the patient is withdrawing from more than one family of drugs. For example, narcotic addicts may be adequately treated with methadone to lessen the withdrawal syndrome from narcotics but then have a grand mal seizure from barbiturate or alcohol withdrawal. Finally, it is to be emphasized that illicit drug users are at risk for tetanus and that this is preventable by immunization, which should be renewed when the patient comes in contact with the medical health care delivery system.

A final comment seems necessary in light of a recent important report[3] suggesting that many physicians have deficient knowledge of the pharmacology and toxicology of narcotic drugs. A recent review has suggested that many physicians underestimate the effective dose range, overestimate the duration of action and exaggerate the dangers of addiction for medical patients receiving narcotics for therapeutic benefit. It would be a great disservice to our patients to be so overly concerned by the changing incidence and medical complications of illicit drug use that we undertreat patients with narcotics and thereby cause needless suffering. Hence physician awareness must extend to the level of the pharmacology of narcotics and other illicit drugs as well as guarded skepticism concerning the reported changing incidence of these medical complications.

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Public Confidence in the Medical Profession

IT WAS MOST HEARTENING to read a recent report in the daily press of a survey of the California public's confidence in many of society's basic institutions and to note that the level of confidence of the California public in the medical profession is very high, exceeded only by research scientists and interestingly enough, the local police department. The report indicated substantially less public confidence at present in such other basic institutions as the Supreme Court, Congress, the news media, colleges, churches, the public school system, organized labor or the State Legislature.

These findings suggest that, in California at least, organized medicine has made some real progress in gaining public understanding and appreciation of its efforts in the field of health care. They also suggest that there may be more public support for what the medical profession in California is trying to do than has been generally realized, and further that the medical profession in this State at least is now on its way to becoming recognized in the role of physician to society as a whole.

The trust and confidence of a patient places a great responsibility upon any physician. The evident and apparently growing trust and confidence of the California public in the medical profession of this State as one of society's basic institutions places a great responsibility not only upon individual physicians but upon the California Medical Association as the primary organizational instrument of California's physicians. It would seem that now may be the time to begin to develop further the concept and the role of the organized medical profession as "physician to society."

—MSMW

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Some Problems in Assuring the Professional Competence of Physicians

We are entering a period of professional and public examination of what is involved in assuring the continuing professional competence of practicing physicians. Until about 1910 there was little done to assure professional competence. Following the Flexner Report of that year, there gradually developed an elaborate system of voluntary accreditation of medical education and later an equally elaborate system for the certification of specialists which ultimately included family physicians. This voluntary system served well and produced physicians of the very highest levels of professional competence. But it could not assure these levels for all practitioners, nor did it particularly address itself to the needs of patients or of the public for physicians' services. Further it assumed that if a physician were once found competent, he would always be so. The time has now come when this is no longer tolerable to the profession or to society, and the whole issue of assuring the professional competence of physicians is undergoing renewed study with particular emphasis on finding means of assuring that their competence is maintained as they go through a lifetime of practice.

The approaches so far have been cautious, and rightly so. Just what should be done is not clear. It is tempting to think simply in terms of renewing an automobile driver's license. Here a vision test and occasionally a physician's certificate to indicate physical capability, a written examination to assess knowledge of the rules of the road, and perhaps a road test to assess performance are required. Airline pilots must pass periodic physical examinations, take periodic refresher training and occasionally have their performance in flight inspected by a peer or supervising pilot. Is there any analogy here for medicine? Perhaps so. Certainly a practicing physician should not be ill either mentally or physically, he should be up to date in his professional knowledge and surely he should perform effectively. If these are among the elements of continuing competence for physicians, then how are they and other essentials to be assessed, and how is their continuing presence to be assured to the profession and the public?

At present there appear to be four principal approaches to assuring continuing professional competence in medicine. Each has serious shortcomings. They are briefly as follows:

1. Legislatures are considering *relicensure,* and specialty boards recertification. If this were done simply by reexamination, a physician would probably have to spend much valuable continuing education time reviewing things he already knows and keeping up with things which are likely to affect his practice little if at all. Important weaknesses in his own knowledge and experience may well go undetected and uncorrected.

2. *Self-assessment tests* have been developed by several specialty societies. These get at what fellow specialists think a physician ought to know within the framework of a given specialty. By taking such a test a physician can identify what of this he may not know, and this makes possible much more efficiency in the use of his continuing education time. But it does not measure his performance in any way.

3. *Practice audits* are a third approach. These do seek to assess a physician's performance in hospital, office or other practice situation. The means of doing this are still in an early stage of development, but as greater sophistication is achieved this approach will certainly become increasingly important. Of course practice audits should be linked to continuing education. It is worth noting that the new patient audit accreditation program of the California Medical Association, which is linked to continuing education, is a leading pioneer in the development of this approach.

4. A fourth way is that of the Continuing Education Certification program of the CMA. It assures that a physician spends a *certain number of hours* within a given time in various kinds of continuing education, the subject matter being selected by the physician himself. This is the most practical approach at this time. But it has weaknesses. It fails to identify what knowledge a physician may be lacking and should have for his particular practice (he may not even know the knowledge exists), nor does it assess his actual performance in practice, and these are both important. However, the wide acceptance of the CMA program

by all concerned attests its very great practical usefulness in the present state of the art.

There are other problems in assuring the continuing professional competence of physicians which require attention. For instance, what value is to be given to the knowledge gained from experience? This increases continually throughout a lifetime of service to patients and surely it is continuing education and surely it contributes importantly to continuing competence. And what about the physically or mentally impaired physician whose problems are often so difficult to identify and even more difficult to solve? More, what can be done about the physician who fails to measure up by whatever criteria? His right to practice is granted him by society, his hospital privileges are granted him by the medical staff and the hospital governing board, and his patients give him the authority to diagnose and treat their ailments. And what are the legal rights of a physician who is deemed by some authority or other not to measure up? These are questions which constantly arise and they are not easily answered; but fair and adequate answers which protect the proper interests of all concerned must be found if the public and the profession are to be satisfied and the continuing competence of a practicing physician is to be assured. There is much to be done and it is particularly appropriate that CMA is to be found at the forefront of progress in this complicated field.

—MSMW

CORRECTION

In the article, "Prevention of Smallpox in Alta California During the Franciscan Mission Period (1769-1883)" by Rosemary Keupper Valle, PhD, July 1973, pages 73-77, Figure 1 was so severely cropped that the lancet mentioned in the caption was not shown. To the right is the picture as it should have been printed.

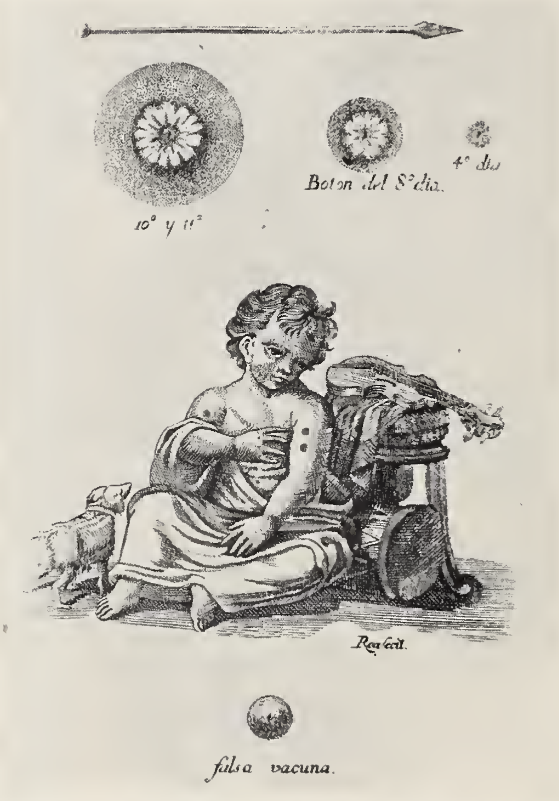
10° y 11°
Boton del 8° dia.
4° dia
falsa vacuna.

Figure 1.—At top is the type of lancet in use at the time. Also shown is the appearance of the pustules at 4, 8, and 10 and 11 days after vaccination. Subject has received multiple vaccinations. At the bottom is appearance of false vaccination.

Gazeta de Mexico, April 1804—*Courtesy of Bancroft Library*

CASE REPORTS

Refer to: Feitelson PJ, Junkin AB: False-positive FTA-ABS test in a heroin addict. Calif Med 119:73-74, Aug 1973

A False-Positive FTA-ABS Test in a Heroin Addict

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NARCOTIC ADDICTION is a major cause of biologic false positive reactions for syphilis.[1-4] Specific treponemal tests are utilized to separate false reactors from addicts with true syphilis. We report a case in which a false positive reaction to a fluorescent treponemal antibody-absorption test (FTA-ABS) led to needless therapy and a useless search for contacts.

Report of a Case

A 20-year-old man heroin addict underwent premarital VDRL testing. He used no heroin during the three weeks before his first test in November 1971, which was non-reactive. A second test was needed in January 1972, when he moved to another state. This time he was taking heroin regularly up to the day of testing. The VDRL was reactive at 1:64. An FTA-ABS test was reactive at 1:1, and the patient was treated with penicillin.

In May, after three weeks of abstinence from heroin, a third VDRL test was non-reactive. He returned to heroin for another four months but decided to enter a drug rehabilitation program in October. Ten hours after his last injection a fourth VDRL was reactive at 1:4. The FTA-ABS test was non-reactive. The patient denied any symptoms of primary or secondary syphilis. Except for multiple needle marks, results of physical examination were within normal limits. Additional laboratory data included normal serum protein electrophoresis, bilirubin, SGOT and alkaline phosphatase.

Comment

Association of a reactive VDRL test with recent heroin usage was striking in this case, though not unusual. False reaction to the VDRL and other non-treponemal tests have occurred in 20 to 25 percent of large series of narcotic addicts.[3,4] To our knowledge, however, false positive FTA-ABS reactions have not been reported in these circumstances.

The FTA-ABS test was reviewed by Sparling.[5] False positive FTA-ABS results have occurred in systemic lupus erythematosus,[6] pregnancy,[7,8] in rare cases of diabetes,[9] following smallpox vaccination,[10] and in certain hyperglobulinemic and dysglobulinemic states.[11,12]

There are two reports of narcotic addicts in whom the possibility of false positive FTA-ABS reactions was at least suggested. Harris and Andrei were unable to categorize 52 of 520 addicts, using Reiter protein complement fixation (RPCF), FTA-ABS, and treponema pallidum immobilization (TPI) tests.[2] An unstated number of these tests contradicted each other. Positive FTA-ABS tests may have been in doubt when associated RPCF and TPI results were negative. Harris and coworkers[3] intimated that specific treponemal tests (RPCF, TPI, FTA, and TPCF) as well as non-specific ones may change from positive to negative following withdrawal from narcotics. While no statistics of reversion of the FTA-ABS test itself were given, any such reversions presumably followed falsely positive tests.

In our case the first reactive VDRL should have been considered falsely positive. Just two months earlier, a VDRL had been negative, and no evidence of primary or secondary syphilis developed while the titer was 1:64.

The low titer of the reactive FTA-ABS (1:1)

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was a clue that it, too, was falsely positive.[11] With borderline and weakly reactive FTA-ABS results, Sparling recommended repetition of the test and further confirmation with a TPI. Absorbing the test serum with an extract of whole Reiter treponeme can eliminate some false positives. Mackey et al used this modification to establish false positive FTA-ABS results in four of five problem cases.[11] In this case the non-reactive FTA-ABS nine months later finally negated the possibility of syphilis.

The patient's history in the present case was also difficult to perceive. When the VDRL and FTA-ABS were reactive (January), questions dealing with his sexual activity led to a list of fictitious contacts. While this story covered his addiction, it deceived his physician into treating him for syphilis and obliged the Health Department to undertake a useless search for contacts.

We cannot speculate on the mechanism by which narcotic addiction causes falsely reactive tests for syphilis. This case suggests a temporal relation between heroin usage and false serologic reaction.

Summary

Reactive VDRL and FTA-ABS tests led to treatment for syphilis in a 20-year-old heroin addict. He contrived a history that provoked a useless search for contacts. Further testing showed that each result was falsely positive.

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Refer to: Leeds SE, Benioff MA, Ortega P: Pulmonary lymphangiomyoma with renal angiomyolipomas—Calif Med 119:74-78, Aug 1973

Pulmonary Lymphangiomyoma with Renal Angiomyolipomas

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LYMPHANGIOMYOMA IS A RARE DISEASE of the lymphatic system in which smooth muscle cells of the walls of the lymphatic vessels proliferate in the lung, mediastinal and retroperitoneal tissues. It is apparently benign, since metastasis has not been reported, but it may cause fatal pulmonary insufficiency. Cornog and Enterline[1] reported six cases of their own and collected 14 from the literature. They listed the following terms used to characterize this group of cases: lymphangioma, lymphangiomyoma, lymphangiopericytoma and leiomatosis. They favor the term lymphangiomyoma, as does Pamukcoglu.[2]* Cornog and Enterline described both a diffuse form of the disease and one which is localized to the mediastinum or retroperitoneum. Since their report of 20 cases, reports of nine more cases have appeared in current medical journals available.[2-10] To the best of our knowledge the present case is the thirtieth.[11]

Although the lesion is rare, new cases are being reported with greater frequency. Early diagnosis may aid in stimulating the development of new forms of treatment and in improvement in the poor prognosis of the diffuse form of the disease. The patient whose case is reported here had renal lesions (angiomyolipomas) such as have been reported in one other patient with lymphangiomyoma and not uncommonly with tuberous sclerosis.

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Submitted August 25, 1972.

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*One reviewer of the manuscript considered lymphangioleiomatosis a better term since lymphangiomyoma suggests a localized tumor.

Report of a Case

The patient, a woman 37 years of age, was well until August 1964 when, after giving birth to her second child, she began to have shortness of breath and to tire easily. In July 1965, a respiratory infection associated with fever and cough developed. The cough and fever subsided, but she had persistent mild shortness of breath. An x-ray film of the chest taken at this time showed a small left pleural effusion. There were increased linear markings with a reticular pattern suggestive of honeycombing throughout the lower half of the right lung field and the lower two-thirds of the left lower lung field. No diagnostic studies of this pleural effusion were performed. By September 1965, the effusion had decreased and it then remained stable for several months.

The patient was first admitted to this hospital in June 1966, with shortness of breath, a slight cough and roetgenographic findings of an increased pleural effusion. She specifically denied chest pain, sputum production, fever and hemoptysis. Her weight was stable. The physical examination was unremarkable except for evidence of left pleural effusion.

On thoracentesis 450 ml of chylous fluid was withdrawn from the left side of the chest. The fluid contained 2,290 leukocytes per cu mm, of which 52 percent were filamented and 48 percent were lymphocytes. Total lipid content was 2,170 mg per 100 ml. Cultures of the fluid were negative for tuberculosis and fungi. A skin test with intermediate purified protein derivative was positive while histoplasmin and coccidioidin skin tests were negative. The patient was discharged without determination of the cause of the chylous pleural effusion.

For a time afterward shortness of breath lessened somewhat and the patient had no particular complaints until February 1967, when increased fatigability and shortness of breath again recurred coincident with a further increase in pleural fluid.

Early in March 1967 she was readmitted to the hospital and 1,000 ml of milky fluid was aspirated from the right side of the chest. The fluid reaccumulated and on March 27 another 1,000 ml of fluid, milky and pinkish, was removed. Physical examination and laboratory studies again were within normal limits except for the finding of left pleural effusion. There were no neurological signs or symptoms. Supraclavicular and femoral lymph node biopsy showed only mild fibrous scarring. An exploratory thoracotomy was advised for definite diagnosis and for control of the recurrent chylothorax.

Right postero-lateral thoracotomy was performed through the bed of the resected seventh rib. The right lung had a uniform cobbled surface (Figure 1) due to innumerable subpleural blebs. The pleural cavity contained about 1,000 ml of milky fluid. The mediastinal pleura was carefully examined and no chyle leak was found. The mediastinal pleura was opened between the diaphragm and the azygous vein and biopsy specimens were taken of the thoracic duct, which showed extensive intramural invasion by spindle-shaped cells (Figure 2). Approximately 3 to 4 cm above the diaphragm were two large succulent,

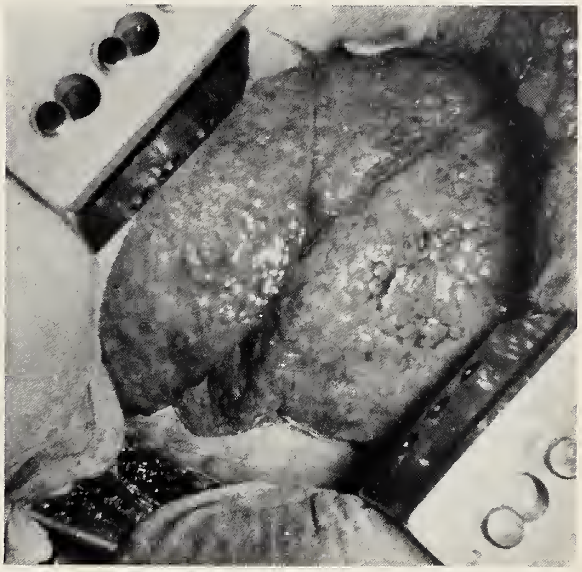

Figure 1.—Cobbled appearance of the right lung seen at operation. The nodules are formed by numerous small emphysematous cysts.

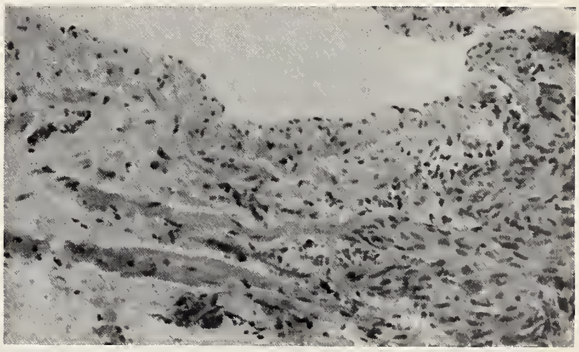

Figure 2.—Lumen of thoracic duct is lined by a thin endothelium. Encroaching cells in lower field of photograph are growing within the muscle layers as solid sheets of spindle cells. (125 ×. Hematoxylin and eosin stain.)

reddish-purple posterior mediastinal lymph nodes and these were removed for histologic examination. Finally, a biopsy specimen of the right middle lobe was taken before the chest was closed.

The patient continued to have respiratory distress and her condition progressively deteriorated because of respiratory insufficiency. She died ten weeks after operation.

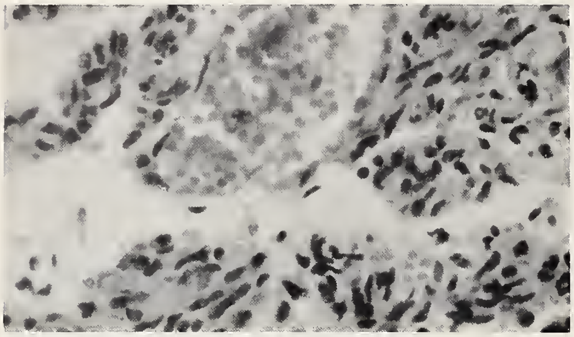

Figure 3.—Clusters of cells growing along pulmonary alveolar septa and around smaller pulmonary vessels. There has been a local total replacement of normal pulmonary tissue. (310 X. Hematoxylin and eosin stain.)

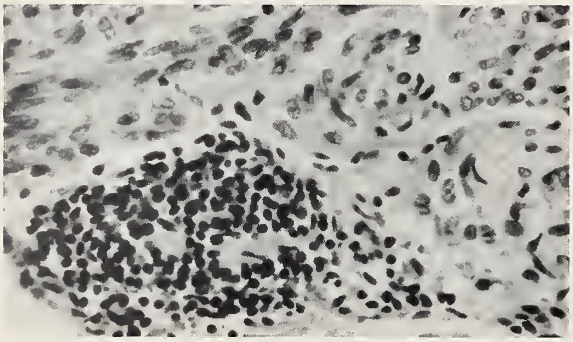

Figure 4.—Almost total replacement of mediastinal lymph node by spindle-shaped cells. Only a single residual collection of small lymphocytes is present. The infiltrating cells appear either elongate or circular, depending on angle of sectioning. (310 ×. Hematoxylin and eosin stain.)

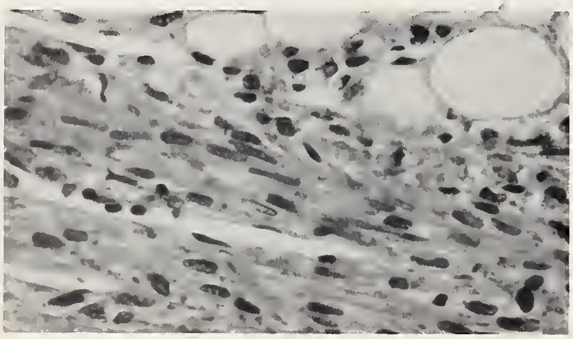

Figure 5.—Renal tumor composed of elongate cells admixed with mature fatty elements. There is a paucity of mitoses. (310 ×. Hematoxylin and eosin stain.)

Pathologic findings. The pleural cavities were almost completely obliterated by dense adhesions. There was a semiloculated collection of approximately 500 ml of a cloudy brownish fluid on the right.

The left lung weighed 800 and the right 900 grams. Innumerable small blebs covered the surface of the lungs, and cut sections of the lungs showed sponginess consistent with a multiplicity of small cysts. There was some focal interstitial condensation of tissue between the cysts, while the hilar structures and lymph nodes were grossly normal.

The heart weighed 260 grams. The left ventricle was normal while the right ventricle was decidedly dilated and contained an apical mural thrombus.

The kidneys were normal in size and configuration but within the cortex there were several small encapsulated white nodular masses which measured up to 1.5 cm in diameter.

The thymic region was unremarkable. Immediately anterior to the abdominal aorta there were several aggregations of a pinkish white tissue.

Permission to examine the brain was not given.

Histological findings. The alveolar structure (Figure 3) was distorted by an admixture of atelectasis and cystic transformation (honeycombing) interspersed with solid fascicles or sheets of cells which were spindle-shaped and contained abundant cytoplasm and slender regular nuclei. Mitoses were rare. Tumor infiltration showed a predilection for lymph nodes, for hilar lymphatic vessels (which were dilated), for pleural surfaces and for interlobular septa. There was a striking tendency toward formation of nodular tumors. The pulmonary parenchyma was extremely edematous and congested with areas of recent bleeding. The tissue from the left lower lobe contained many emboli and evidence of infarction.

Many lymph nodes from the chest and abdomen demonstrated a partial or complete replacement by spindle-shaped cells (Figure 4). These changes were especially pronounced in the retroperitoneal nodes about the celiac axis. The pink masses of tissue anterior to the abdominal aorta were lymph nodes which were massively replaced by proliferating bundles of spindle-shaped cells.

The renal cortical lesions were also composed of similar spindle cells plus mature fat cells, giving them the appearance of angiomyolipomas (Figure 5).

TABLE 1.—*Classification of 30 Cases of Lymphangiomyoma*

	No. of cases
I. Diffuse lymphangiomyoma involving lungs, usually with mediastinal and retroperitoneal lymph nodes (nine of these cases also had lymphangiomyomatous masses in mediastinum or retroperitoneum)	18
II. Diffuse lymphangiomyoma in the posterior mediastinum or retroperitoneum or both without lung involvement	1
III. Circumscribed lymphangiomyoma in	
(a) mediastinum	7
(b) retroperitoneum	0
(c) both mediastinum and retroperitoneum	1
IV. Lymph node in	
(a) mediastinum	2
(b) retroperitoneum	1
(c) both mediastinal and retroperitoneal	0
TOTAL	30

Note: The only male was in Group III-c.[13]

In summary, autopsy findings showed diffuse smooth muscle cell proliferation with a multifocal distribution in lung, mediastinum and retroperitoneum. Severe generalized pulmonary alveolar septal involvement was associated with cystic transformation (honeycomb lung), pulmonary and pleural fibrosis and right ventricular hypertrophy. Some nodes were only partially infiltrated with spindle-shaped cells, suggesting an earlier stage of involvement.

Comments

Recent reviews and case reports have described in detail the varied clinical and pathologic features of diffuse lymphangiomyoma[1-11] with emphasis on the association of chylothorax, honeycomb lung and posterior mediastinal and retroperitoneal lymph node infiltration with smooth muscle cells. A striking sex incidence (29 of the 30 reported cases were in women) suggests that hormones may have a place in the treatment of the disease. In fact hormones were used in one case.[8]

The most common roentgenographic finding is pleural effusion, which may be unilateral but is frequently bilateral. On thoracentesis chylous fluid is obtained. Spontaneous pneumothorax occurred in one-fourth of the patients. The lungs show a fine reticulonodular interstitial infiltrate distributed diffusely and uniformly throughout the lung fields. At a more advanced stage small cysts are formed, giving the appearance of "honeycomb" lungs.[11] With publication of the paper of Laipply and Sherrick[12] in 1958, this disease entity became more clearly distinguishable from the relatively more frequently occurring smooth muscle hyperplasia of the lung (honeycomb lung) associated with chronic pulmonary infection or granulomatous disease. Cornog and Enterline[1] described the pathologic changes in detail and considered the lesion a hamartoma, often of multifocal origin. The lesions in the lungs and mediastinum bear a striking resemblance to lesions found in certain cases of tuberous sclerosis. However, there is only one report[6] of tuberous sclerosis of the brain in a patient with lymphangiomyoma.

The 29 cases reported to date,[1-10] and the present case fall into four groups (Table 1) when classified by pathologic findings. In some cases the information about the patient is incomplete and therefore classification cannot be exact. It is possible, as Bush et al[8] have pointed out, that the diffuse disease (Group I and II) is a different disease entity from localized disease (Group III and IV). Group I is characterized by muscular disease of the lung frequently accompanied by chylothorax, and by a peculiar type of mediastinal or retroperitoneal lymph node involvement. Eighteen of the reported cases are in this category, and in nine of them there were also lymphangiomyomatous masses in the mediastinum or retroperitoneum. The single patient in Group II had diffuse involvement of the retroperitoneum without involvement of the lung. Groups III and IV include the cases in which the lesions are encapsulated or are in isolated lymph nodes in the mediastinum or retroperitoneum. Such cases may be treated curatively by surgical extirpation. The only case in a male was in Group III(c).

There were 12 patients in Groups II, III and IV. One had died, eight had been living for from one to fourteen years at the time of report, and the outcome was not mentioned in two. The single known death in Groups II-IV was in the only male patient; it occurred after development of bilateral pneumonia thought to be due to aspiration of fluid.[13] However, diffuse pulmonary infiltrate had been present before the operation, and after operation roentgenographic evidence of interstitial pneumonitis developed. An alternative interpretation is that the pulmonary disease was secondary to lymphangiomyoma rather than to aspiration.[1]

Of special interest in the present case were the renal cortical tumors which have been reported in one other case of lymphangiomyoma (reported by both Cornog and Enterline; Case 6, and Vadas and coworkers; Case 3). Renal angiomyolipomata occur rarely in the general population but are not uncommon in patients with tuberous sclerosis.[14-16] This tumor is of special interest to urologists, since it may displace the pelves and calyces of kidneys and simulate a malignant tumor, or, when multiple and bilateral, may simulate conditions associated with polycystic kidneys.

Summary

A case of diffuse lymphangiomyoma, believed to be the thirtieth of record, is reported. Characteristic features of the disease are its predilection for women; occurrence in a localized form which is curable by complete surgical excision, or in diffuse form which progresses to death from cardiorespiratory failure; and onset with dyspnea, recurrent pleural effusions, spontaneous pneumothorax and chylous effusions in serous cavities. Pathologically it is considered to be a hamartoma, often of multifocal origin. Renal angiomyolipoma, reported in only one other instance, was present.

Treatment and prognosis are different for the localized than for the diffuse forms of the disease.

ACKNOWLEDGMENT

Drs. H. T. Enterline and H. Z. Klein reviewed the pathologic material and confirmed the diagnosis.

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Refer to: Costanza DJ, Hoversten VW: Accidental ingestion of water hemlock—Report of two patients with acute and chronic effects. Calif Med 119:78-82, Aug 1973

Accidental Ingestion of Water Hemlock

Report of Two Patients with Acute and Chronic Effects

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WATER HEMLOCK is probably the most poisonous plant that grows in the United States. It is extremely toxic to livestock and to man. In two cases of severe poisoning in humans, the acute phase was manifested by convulsions, uncontrolled neuromuscular movements, respiratory distress, cardiovascular variability, and metabolic acidosis. The long-term chronic effects were electroencephalographic abnormalities and anxiety neurosis.

The toxic effects of cicutoxin in man were first recorded by Wepfer in 1679.[1] He reported several children poisoned by the Cicuta hemlock plant and noted "noncoagulation of the blood." In 1814 Stockbridge[2] reported three cases, which were the first in the United States; two of the patients died during violent convulsions. In 1911, Egdahl reviewed the literature and found reports of 47 cases in Europe and the United States.[3] The frequency of reports is now much greater and shows that cicutoxin toxicity is still a severe health hazard especially to children. Within the past two years two other reports from divergent areas of the country attest the continued danger of exposure,[4,5] and poisonings are still reported in Europe.[6] Two cases of accidental ingestion of large amounts of cicutoxin, in which the patients survived but had long-term aftereffects, are reported herein.

In 1969, five boys were hiking in the hills of

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Marin County, California, when they became hungry and saw a plant that was similar to a known wild edible plant. Two ate several bites of the root (rhizome), which tasted like sweet wild anise, two tasted it and spat it out, and the fifth refused to taste or touch it. Approximately 20 to 30 minutes after ingestion the two boys, who were brothers, became nauseated while driving in the car. They started to salivate, had stomach cramps, and vomited repeatedly. At a nearby gasoline station both boys began to have repeated grand mal seizures. First aid was given and the police delivered the boys to the Emergency Room at Marin General Hospital.

CASE 1. A 15-year-old Caucasian boy was admitted to Marin General Hospital 31 January 1969, 30 to 45 minutes after ingestion of two or three rhizomes of the water hemlock plant, Cicuta virosa. The patient was cyanotic, had widely dilated pupils, and was in obvious respiratory distress. Blood pressure was 130/80 mm of mercury and pulse 120 beats per minute in supraventricular tachycardia. An oral pharyngeal airway was inserted. The patient began to have convulsions and 100 mg of phenobarbital and 100 mg of sodium diphenylhydantoin (Dilantin®) were given intravenously, and intravenous infusion of a solution of Ringer's lactate was started. A Foley catheter was inserted into the bladder. The cyanosis disappeared, respiration was labored, and naso-tracheal airway intubation was accomplished. A Bird Mark VII respirator was applied and respiration was continuously monitored. Blood pressure fluctuated between 80/60 and 170/90 mm of mercury and the heart rate varied from 50 to 120 beats per minute. The skin was warm and dry. The muscles were rigid and the pupils dilated widely and then constricted spontaneously. There were also periods of opisthotonos with severe rigid muscle spasms. All of these symptoms were observed repeatedly and seemed to have no relation to each other—they seemed to vary independently. Convulsions continued and pentobarbital sodium, 100 mg, was given every 30 minutes intravenously.

After lavage of the stomach, a universal antidote was instilled, and then 8 ounces of potassium permanganate 1:1000 in solution was left in the stomach for 45 minutes and withdrawn. Five percent sodium bicarbonate, 200 ml, was then instilled in the stomach and withdrawn. Convulsions continued intermittently despite treatment with pentobarbital sodium.

About an hour after admission a slight flush developed around the face and neck. Fluctuation of the pupils, clenching of teeth, severe muscle spasms and rigidity, and periodic episodes of severe opisthotonos and intermittent hemiballismic motions continued. Bilateral ankle clonus was present but Babinski and Hoffman reflexes and Wartenberg's sign were absent. The patient was restless and thrashed about. Sodium pentothal, 50 mg, was administered intravenously about 90 minutes after admission; the thrashing diminished in severity, but the convulsive disorder continued. After toxicologic consultation, 3 ml of paraldehyde was administered intravenously over a ten-minute period and the convulsions stopped. Blood pressure finally stabilized at 130 to 140/78 to 86 mm of mercury approximately two hours after admission. Maintenance doses of phenobarbital sodium, 60 mg intramuscularly every six hours, were started. Once the convulsions were controlled, the alternating bradycardia and tachycardia subsided, although the cardiovascular events were not directly correlated with the convulsive disorder. The electrocardiogram taken during the convulsive period was within normal limits, showing only sinus arrhythmia.

Laboratory data on admission were as follows: serum sodium 137, potassium 3.8, and chloride 99 mEq per liter, carbon dioxide combining power 7 mM per liter, phosphorus 2.2 mg per 100 ml, alkaline phosphatase 1.8 Bodansky units, creatinine 1.1 and blood urea nitrogen 13.0 mg per 100 ml. Bilirubin, amylase, calcium, glucose, albumin, and globulin were within the normal range. Leukocytes numbered 17,800 per cu mm with 62 percent lymphocytes, and the platelet count was normal. The prothrombin time was 15 patient seconds/12.5 control seconds on admission, but follow-up measurements were normal. The serial changes in serum glutamic oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH) and creatine phosphokinase (CPK) are summarized in Table 1.

Urinalysis revealed transient 2+ proteinuria; 5-hydroxyindoleacetic acid was normal at 3.1 mg in 12 hours.

The patient was rousable after ten hours, but not completely awake until approximately 24 hours after ingestion. He complained of soreness all over his body, particularly in the muscles of the arms and legs. He thought his mind was a little fuzzy but he was not sure about this. An electroencephalogram was very abnormal, showing generalized excess of slowing throughout and a large amount of paroxysmal discharging, more prominent over the frontal areas and exhibiting alternating lateral predominance. A Neurologic Index of Mental Impairment (NIMI) test[7] revealed severe organic mental impairment. There was a steep rise in the levels of creatine phosphokinase and lactic dehydrogenase, which was attributed to muscle trauma secondary to convulsions and rigidity. An x-ray film on January 31 and a second electrocardiogram on February 2 showed no abnormalities. Before the patient was discharged, peeling of the skin on palms and soles was noted. The patient was discharged and Dilantin, 100 mg orally three times a day, and phenobarbital, 15 mg orally four times a day, were prescribed.

Approximately a week after discharge the patient had an acute anxiety reaction and was seen by a psychiatrist. He had hallucinations and visual flashes of white and purple and complained of a feeling of nausea when his eyes were closed. His symptoms were considered partly due to organic flashback and partly due to anxiety neurosis. Approximately three weeks after discharge the patient stopped taking the medications, against medical advice. Results of the two follow-up electroencephalograms and NIMI tests obtained on 11 February and 29 September 1969 were still very abnormal. The last NIMI test showed improvement with a score of 68 percent (normal for 12 years and older, 86 ± 7 percent), indicating mild loss of intellectual functioning for his age and grade level. The electroencephalogram on 29 September 1969 was mildly abnormal, showing pronounced improvement with only slight degeneralized and paroxysmal cerebral dysrhythmia.

CASE 2. A 14-year-old Caucasian boy was admitted to Marin General Hospital 31 January 1969 about 45 minutes after ingestion of part of one rhizome of Cicuta virosa. The patient was convulsing, cyanotic, and comatose. Blood pressure was 138/60 mm of mercury, pulse 84 beats per minute, and respirations wheezing in character between convulsions. Bowel sounds were audible without a stethoscope. The facial skin was flushed. An endotracheal tube was inserted immediately and an intravenous infusion of Ringer's lactate solution was started. The stomach was washed with 8 ounces of potassium permanganate solution 1:1000, and then a 5 percent sodium bicarbonate solution was instilled into the stomach and withdrawn. Simultaneously with the lavage, amobarbital sodium, 0.5 grams, was administered intravenously. Because of persistent convulsions, penthothal sodium, 50 mg, was given intravenously three times about 15 to 30 minutes apart. About an hour and a half after admission the blood pressure was 70/60 mm of mercury but increased spontaneously without vasopressors to 100/70 mm. Because of another convulsion, phenobarbital sodium, 120 mg, was administered intramuscularly. The wheezing and hyperactive bowel sounds ceased and the pupils became normal in size. The convulsions stopped completely about three and a half hours after admission, but the patient became very active, clenching his teeth, swinging his arms randomly, arching his back, and moving his whole body continuously. He was not responsive to commands. Intramuscular administration of paraldehyde, 3 ml, and another dose of phenobarbital sodium, 120 mg, did not appear to affect the hyperactivity. Therefore, diazepam (Valium®) was administered both intravenously (5 mg) and intramuscularly (5 mg). (By differing the regimen from that followed in Case 1, it was hoped to determine the best means of controlling the recurrent convulsions.) Repeated doses of Valium appeared to control the excessive activity in about 30 minutes. Eight hours after admission

TABLE 1.—*Laboratory Data Obtained on Admission and Subsequently in Both Patients*

	Date (1969)						
Constituent (unit)	*1/31-7:00 pm*	*2/1*	*2/2*	*2/3*	*2/4*	*2/11*	*2/12*
CASE NO. 1							
SGOT (normal 50 units)	60	..	180	..	266	30	..
LDH (normal 200 units)	570	..	590	..	720	380	..
Creatine phosphokinase (normal 30 units)	103	..	1200	..	2400	38	..
CASE NO. 2							
SGOT (normal 50 units)	106	18	..	1180	1060	..	40
LDH (normal 200 units)	700	1060	..	1870	1290	..	..
Creatine phosphokinase (normal 30 units)	99	128	..	2380	4000	..	56

the patient continued to have intermittent prominent flushing of the face and body, but a 12-hour urine test revealed a normal level of 5-hydroxyindoleacetic acid.

Laboratory data on admission were as follows: serum sodium 144, potassium 4.1 and chloride 104 mEq per liter, carbon dioxide combining power 7 mM per liter, phosphorus 2.7 mg per 100 ml, alkaline phosphatase 3.0 Bodansky units, creatinine 1.5 and blood urea nitrogen 13 mg per 100 ml, and amylase 375 Somogyi units per 100 ml. Glucose, calcium, bilirubin, albumin, and globulin were all within normal limits. Leukocytes numbered 21,000 per cu mm with 58 percent lymphocytes, and the platelet count was within normal limits. The leukocyte count returned to normal by the fifth day. Serial changes in SGOT, LDH, and CPK are summarized in Table 1.

About 30 hours after admission the patient wakened enough to ask what had happened. His muscles were very sore and the skin on his face was scaling almost as if he had been sunburned. Both conditions lasted for several days. On the second hospital day his temperature rose from normal levels to 39.4°C (103°F) and rhonchi were heard in his chest. The chest roentgenogram was clear but Hemophilus parainfluenza was cultured from the throat. Tetracycline therapy, 500 mg four times a day, was carried out until all evidence of infection disappeared. On 4 February 1969 an electroencephalogram showed prominent variable slowing throughout, with irritative features, and a NIMI test revealed decided intellectual impairment. Although still weak, the patient was discharged February 13. At this time both the creatine phosphokinase and serum glutamic oxaloacetic transaminase levels were still a little above the normal range. With the exception of occasional nightmares, no specific psychiatric problems occurred after discharge but an electroencephalogram taken 27 February 1969 was still abnormal although the NIMI test taken at the same time was within normal limits.

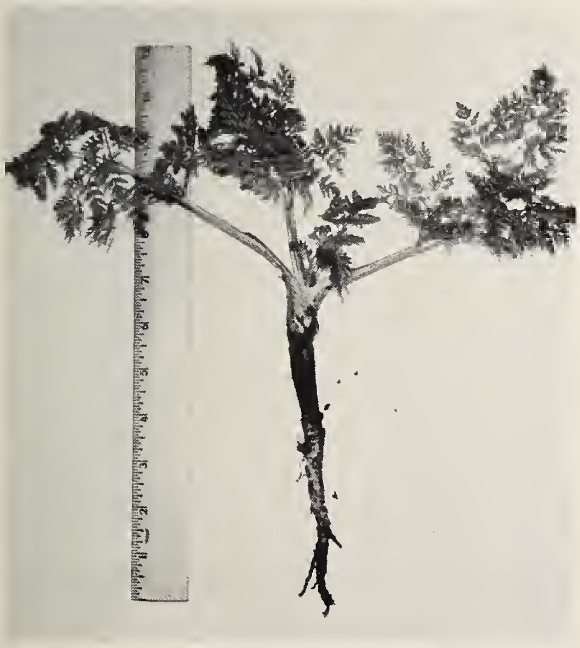

Figure 1.—Young Cicuta virosa plant, showing compound leaves and fleshy root. This species grows 8 to 10 feet high.

Discussion

Water hemlock, cow bane, five-finger root, "snake weed," "wild carrot," or Cicuta virosa (Cicuta maculata, Cicuta vagans) is of the botanical family Umbelliferae. It is a perennial plant with large compound leaves and clusters of fleshy roots (Figure 1) and is related to the parsley family. The plants are usually found in marshy ground around ponds or ditches. They may be mistaken for wild parsnips, artichokes, celery, sweet potatoes, and, in our case, sweet anise.[8-16]

Cicutoxin (an unsaturated aliphatic alcohol) is the toxic component of Cicuta virosa and is found in all parts of the plant, but the greatest concentration is in the root stock or rhizome. The usual lethal dose in an adult is one rhizome,[17] although whistles made from the hollow stems of the plant have caused deaths in children.[18] A piece of root the size of a walnut has been known to kill a cow, and a single root has been known to kill a horse.[3]

Usually nausea, salivation, emesis, and tremors develop within 30 to 60 minutes after ingestion. Abdominal cramps and projectile and violent vomiting occur, and severe convulsions ensue.[8,14,19,20] Death results from exhaustion and respiratory paralysis. Retrograde amnesia has been reported to be not uncommon upon recovery,[14,17] but so far as could be determined serial electroencephalograms and tests of mental function have not been reported heretofore.

Clinically we observed previously reported toxic reactions: salivation, nausea, projectile vomiting, abdominal cramps, restlessness, rigidity, opisthotonus, convulsions of severe and violent nature, widely dilated pupils, trismus, and retrograde amnesia. Additional physiologic effects that have not been reported elsewhere were hemiballismic type motion, localized flushing, and subsequent peeling of facial skin and of palms and soles. The pronounced and varied reactions of the cardiovascular system observed in the two cases herein reported, including bradycardia, tachycardia, hypotension and hypertension, agree with clinical observations of Egdahl[3] and Statton[8] and the pharmacologic studies of this toxin by Grundy and Howarth.[21] In addition, Withers et al[5] reported no detectable pulse and demonstrated hypotensive effects in dogs when 95 percent ethyl alcohol extract of hemlock root was administered intravenously.

Of the abnormal laboratory data, the very low bicarbonate level probably resulted from metabolic acidosis and was possibly accentuated by respiratory alkalosis, although plasma pH was not determined. The high creatine phosphokinase levels reflected the severe muscle rigors, rigidity, and convulsions[22] and the lactic dehydrogenase levels also revealed a moderate elevation of LDH isoenzyme fraction 5, suggesting liver or skeletal muscle damage.[23,24] We believe that the persistence of these levels was attributable to severe muscle involvement in the convulsions, although we cannot be certain that direct muscle toxicity was not present. Elevated enzyme levels after convulsions are well known and they have been observed after convulsive shock therapy.[24] The increased prothrombin time in Case No. 1 is unexplained but may be due to liver involvement. Proteinuria was transient and may have been a nonspecific reaction of the toxin.

We found that Valium was more effective than paraldehyde or barbiturates in controlling the severe uncoordinated muscular movements of the acute phase. We were not able to evaluate or compare these drugs adequately with regard to their effectiveness in controlling seizures, but both were effective.[26-30] It was a relief to know that we had drugs to control these seizures and movements which were the wildest and longest convulsions in the experience of those on the medical and nursing staff attending these patients.

We conclude on the basis of the abnormal follow-up electroencephalograms and NIMI tests and the psychiatric evaluation that the toxic effects on the psyche and cerebrum were not transient. Chronic cerebral and psychiatric effects have not been reported heretofore. During the early convalescent period, one patient (Case 1) had dreams, fears, a feeling of non-wellbeing, attacks of acute anxiety, and visual phenomena. The electroencephalograms, NIMI tests, and clinical observations indicated severe organic mental impairment that persisted for several months.

ACKNOWLEDGMENTS

The Fairfax Police Department responded promptly to the emergency and gave excellent first aid. Professor Lincoln Constance of the Department of Botany, University of California, Berkeley, California identified the plant and rhizome, after the California Highway Patrol had swiftly taken them to him.

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Refer to: Falk PM: Constrictive pericarditis presenting as a mediastinal mass. Calif Med 119:83-85, Aug 1973

Constrictive Pericarditis Presenting as a Mediastinal Mass

PETER M. FALK, MD
Los Angeles

Chronic constrictive pericarditis is characterized by pronounced venous distension with severe dyspnea, ascites out of proportion to the dependent edema, muffled heart tones and usually the absence of significant cardiomegaly on x-ray films. As emphasized by Plauth et al[1] a few patients may present with generalized edema and other signs of hypoproteinemia as a result of a protein-losing enteropathy secondary to the pericarditis. Attention has not been drawn to the fact that the radiologic findings consistent with this diagnosis may be substantially altered by associated defects of the pericardium.

The purpose of this report is to describe a 16-year-old boy with chronic constrictive pericarditis who also had a partial pericardial defect. The resultant herniation of the left atrial appendage caused radiologic manifestations highly suggestive of a mediastinal mass lesion.

Report of a Case

A 16-year-old Mexican boy was admitted to the UCLA Medical Center with complaint of "chest pains and chest pounding" of eight months' duration. The chest pain was sharp in character. Five months before admission here, the symptoms had become more severe and were aggravated by physical activity. There was no history of congenital heart disease, heart murmur, cyanosis, rheumatic fever or rheumatic heart disease. The patient was then taken to an orthopedic clinic in Calexico, where he was being followed for paraplegia secondary to poliomyelitis contracted at three years of age. Chest roentgenogram demonstrated a left hilar mass. Tuberculosis was apparently excluded and it was then that he was referred to the UCLA Medical Center for further study.

On physical examination he appeared thin, short and chronically ill, with a protuberant abdomen and mild respiratory distress. He was mildly febrile (37.7°C) with a regular heart rate of 104 per minute, a respiratory rate of 28 per minute, and blood pressure of 90/64 mm of mercury. The blood pressure did not vary abnormally with respiration. Positive physical findings included facial, sacral and lumbar edema, pink nail beds with clubbing of the fingers, and distended veins over the thorax and abdomen. The neck veins were distended and pulsated vigorously. The lungs were clear to percussion and auscultation. No murmurs were heard. The heart tones were somewhat muffled and an intermittent third sound was heard which varied with respiration (this was later believed to be a "pericardial knock"). The abdomen was distended and there was a positive fluid wave. The liver was palpable 3 cm below the right costal margin. Neurological examination was unremarkable except for generalized muscle wasting with paralysis and absence of deep tendon reflexes in the lower extremities.

Laboratory data included hemoglobin of 12.4 grams per 100 ml of blood, a hematocrit of 37.1 percent, a leukocyte count of 6,100 per cu mm, with 81 segmented neutrophils, 2 banded neutrophils, 8 eosinophils, 1 basophil, 7 lymphocytes, and 1 mononuclear cell. Urinalysis was negative and creatinine content was 0.5 mg per 100 ml. The total serum protein was 3.7 grams per 100 ml with albumin of 2.7 grams. Skin tests for coccidioidomycosis, blastomycosis, histoplasmosis, and tuberculosis (with intermediate and second strength purified protein derivative) were negative. A roentgenogram of the chest showed a mass-like lesion in the mediastinum (Figure 1). No abnormality was noted on aspiration of bone marrow. A cardiac scan was consistent with pericardial effusion but a solid mediastinal tumor could not be ruled out. A roentgenographic bone survey showed no metastatic lesions. A barium swallow with fluoroscopy showed the mass to be a pulsating structure which beat paradoxically with the left ventricle. Electrocardiography revealed gen-

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From the Department of Pediatrics, University of California, Los Angeles, School of Medicine.

Submitted October 6, 1972.

Reprint requests to: P. M. Falk, MD, Department of Pediatrics, University of California, Los Angeles, Center for the Health Sciences, Los Angeles, CA 90024.

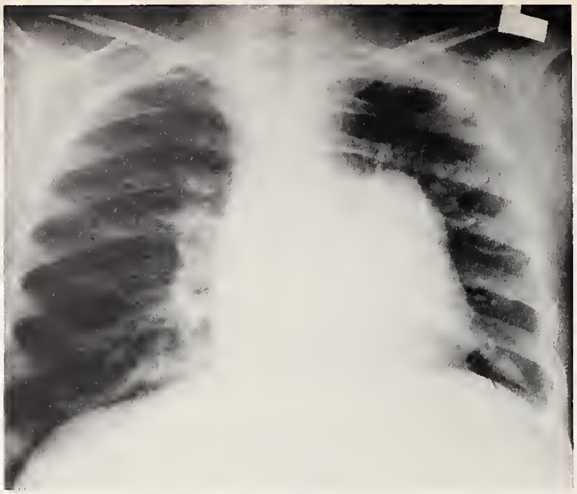

Figure 1.—Teleroentogram showing some cardiomegaly with irregular enlargement of left border suggestive of a mediastinal mass.

eralized low voltage with a prolonged P-R interval. There was evidence of left atrial enlargement (Figure 2).

Cardiac catheterization and angiocardiography demonstrated a large left atrium and aneurysmal dilatation of the left atrial appendage, which appeared to have herniated through a pericardial opening. The antecubital venous pressure was 23 cm of water.

A tentative diagnosis of constrictive pericarditis with partial pericardial defect was made, but some observers felt that a mass lesion was still a possibility. Exploratory operation was recommended and was carried out 17 days after admission. At thoracotomy, thick fibrinous adhesions were found in the left hemithorax. The right hemithorax was free of involvement. There was a tight fibrinous exudate and an adhesive layer between the epicardium and the pericardium. There was herniation of the left atrial appendage through a partial pericardial defect. Radical pericardiectomy was performed. Granulomatous inflammation with calcification and fibrosis of the pericardium was seen on pathologic examination of the surgical specimen. The cause was not established. Postoperatively, congestive heart failure developed and was treated with diuretics, salt-poor albumin, and digoxin. The course thereafter was uneventful. At a later date, acid-fast bacteria were grown from a urine specimen. Also, reexamination of the pericardial pathologic sections revealed the presence of acid-fast bacteria. The patient was discharged with antituberculosis chemotherapy.

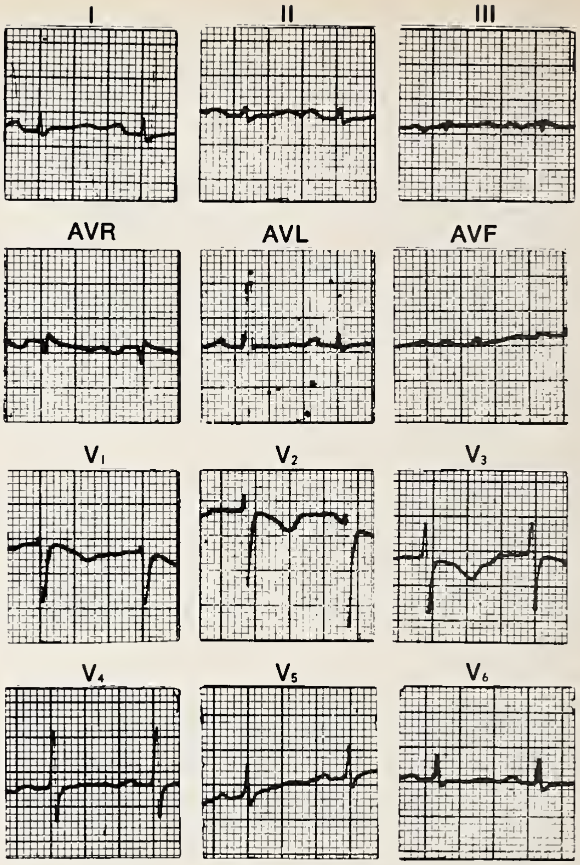

Figure 2.—Electrocardiogram showing decreased voltage in all leads. There is also prolongation of the P-R interval with widening of the P waves suggestive of left atrial enlargement.

Discussion

Constrictive pericarditis is an uncommon pathologic condition in children. According to Jones et al[2] fewer than a hundred cases have been reported in children. The great majority (60 percent) are idiopathic but a significant number (30 percent) are due to tuberculosis.[3]

Pericardial defects are more often found on the left side. They may be partial or total and are congenital in origin. Generally asymptomatic, pericardial defects may be commoner than they are generally believed to be. Abbott's classic review of 1,000 autopsies lists 30 cases of this defect. If symptomatic, they may be associated with vague chest pain and, in rare instances, sudden death possibly due to cardiac herniation and strangulation.[4,5]

The combination of these two conditions has been reported in only one case, that of a 67-year-old woman who was treated successfully by operation.[6] Prominence of the left heart border was observed on a roentgenogram of the chest and was interpreted as indicating left atrial enlargement or dilation of the pulmonary artery segment. Associated constrictive pericarditis was suspected before operation.

The specific cause of the pericarditis in the patient herein reported upon was finally established as tuberculosis. Greenberg et al[6] suggested that the mechanism in the case they reported (non-tuberculous) may have been (1) inflamation of the pericardium resulting from spread of infection from the pleural cavity and (2) adhesions arising from impaired pericardial cushioning during the cardiac cycle.

Chronic constrictive pericarditis is a fatal disease if untreated. It can be corrected surgically, however, and recognition of it is therefore important. When it is associated with a pericardial defect, the radiologic features may be misleading. Although only one previous instance of such an association could be found in the literature, this may not reflect the true incidence, as congenital pericardial defects may be commoner than is generally believed.

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LETTERS *to the Editor*

To Heal or to Treat?

To the Editor: The Report on Euthanasia by the CMA Committee for the Continuing Study of Evolving Trends in Society Affecting Life in the March issue of California Medicine was a timely article that stated the moral and socio-economic issues regarding euthanasia. That this committee is comprised of physicians is obvious from the statement in the last paragraph . . . "it is imperative that medicine maintain its role of *healer*, rather than executioner". "To heal" means: "To make sound or whole, to restore to health, to restore to original purity or integrity, to return to a sound state."[1] The incidence of cancer is one in four in our community, with less than 50 percent of these patients "healed."

Heart disease remains the leading cause of death. Eventually, all people die. How can we be healers? As long as physicians and the public interpret the function of the physician to be a healer, and with this the implied warranty of good health and return to function, then neither the physician nor the public can accept the reality of the physician as being a "treater" rather than "healer."

"To treat," as defined, means "to care for or deal with medically or surgically."[1] Herein lies the responsibility of the physician—to *care* for or deal with medically or surgically, without implied warranty of "cure." To treat suggests an active, positive role of decision-making and treatment commitment entered into by the physician on behalf of the patient. The active process might be in the form of cardiac resuscitation, emergency respiratory assistance, or any therapies for the treatment of the condition considered to have the possibility of returning the patient to good health. The active process might also be in the form of the administration of large doses of narcotics to the patient with a terminal illness wherein suffering is intense, aggravated by the depression of the continued inevitability of his illness until captured by death. The physician has the responsibility to *treat* or take an active part in aiding and providing comfort to the patient and family, rather than denying or prolonging their intense discomfort.

As long as physicians and the public identify the physician's role as "healer," euthanasia cannot be discussed in its proper perspective.

Theodore Cohen, MD
San Jose

REFERENCE

1. Webster's Seventh New Collegiate Dictionary. Springfield, Mass. G & C Merriam Co., Publishers, 1970

On Some Unproven Effects of Aspirin and Saccharine

To the Editor: Recently, two widely used chemicals have been mentioned in the public press, aspirin and saccharine.

Saccharine, used widely by diabetics and the obese, has been indicted as a possible cause of bladder cancer, because of experiments with rats. Some have even proposed removing it from the market. Before further expensive and time-consuming research is done, it would appear prudent to examine the records of diabetics. Diabetics have used saccharine in large doses for half a century. It would be a relatively simple matter to see whether diabetics have a higher than expected incidence of bladder cancer. If they do, of course, we learn nothing because there may be something inherent in diabetes itself that increases the rate of bladder cancer. But if they do *not,* it would seem to remove saccharine as a potential bladder carcinogen.

Aspirin has been proposed as a possible antithrombic agent because it allegedly prevents platelet stickiness. The same logic applies. Rheumatoid arthritics have taken large doses of aspirin for fifty years. Do rheumatoids have less stroke and less coronary thrombosis than the general population? If so, it proves nothing because there may be some protection afforded by the rheumatoid process itself. But if statistics show that rheumatoid arthritics have as much thrombotic disease as anyone else, why probe further?

Arthur D. Silk, MD
Garden Grove

Short Stay Surgical Centers

A Statement by the California Medical Association Commission on Health Facilities

AMBULATORY SURGICAL CENTERS are an experimental way of providing surgical care. They should meet the standards of care set for the surgical departments of general hospitals by the Joint Commission on Accreditation of Hospitals and the Medical Staff Survey Committee of the CMA. Before a center is opened, the following criteria should be established by the center, local medical society and health planning council.

1. There shall be an arrangement for hospital transfer and backup including methods of transportation and communication between center and hospital.
2. There shall be a method of screening patients appropriate for the center.
3. Adequate patient records shall be maintained.
4. There shall be a method of checking the credentials of the physicians practicing in the center and standards set for granting privileges to use the center. In no case shall surgical privileges be granted a physician exceeding those granted to him by any of the hospitals in which he has staff privileges, and these should be consistent with the privileges he holds in various community hospitals.
5. There shall be peer review and reporting to local medical society, and there should be a standing Medical Audit Committee of Physicians who regularly review the procedures and privileges of the staff.
6. Cooperating hospitals shall be in *close* proximity to any freestanding surgicenter. Hospitals, in cooperation with comprehensive health planning, shall be encouraged to develop surgicenters as an integral part of their complex where appropriate.

Approved by the Council of the California Medical Association, May 4-5, 1973.

Selected Items from the FDA Drug Bulletin

Postcoital Diethylstilbestrol

IN AGREEMENT WITH ITS extragovernmental physician-advisers, FDA has approved, under restricted conditions, postcoital (contraceptive) use of diethylstilbestrol (DES), a synthetic estrogen. Adequate evidence to support the use of any other estrogen for this purpose is not presently available.

The Agency considers the use of DES for this purpose to be safe only as an emergency measure (in situations such as rape, incest, or where, in the physician's judgment, the patient's physical or mental well-being is in jeopardy) and explicitly warns against its routine or frequent use as a contraceptive.

Physicians are urged, prior to prescribing DES for this purpose, to inform patients (or guardians) fully of the possible side effects of the drug, and of alternative measures available and their hazards, so that the patient may participate in an informed way in the decision to use the drug. Pregnancy should be ruled out by appropriate tests prior to instituting therapy, so that no unnecessary exposure of a fetus to DES occurs.

The efficacy of DES in preventing pregnancy depends upon the time-lapse after coitus and dosage of the drug. The currently recommended dosage is 25 mg twice a day for 5 continuous days beginning, preferably, within 24 hours and not later than 72 hours after exposure. When this dosage is given within the specified time interval after sexual intercourse, DES is highly effective in preventing conception. But the patient must be warned to take the full course of the drug in spite of the nausea which commonly occurs, if it is to be effective.

There is at present no positive evidence that the restricted postcoital use of DES carries a significant carcinogenic risk either to the mother or fetus. However, because existing data support the possibility of delayed appearance of carcinoma in females whose mothers have been given DES later in pregnancy, and because teratogenic and other adverse effects on the fetus with the very early administration recommended are ill understood, failure of postcoital treatment with DES deserves serious consideration of voluntary termination of pregnancy.

Before prescribing, the physician should be familiar with the complete FDA-approved labeling on products intended for this use.

FDA Drug Bulletin, May 1973

U-100 Insulin

U-100 INSULIN, which is now being made available, offers distinct advantages over U-40 and U-80 preparations. It is offered as regular and in a variety of long-acting forms.

Each milliliter of U-100 insulin contains 100 units of insulin. The drug is dispensed in 10 ml (1,000 unit) vials.

It is important that patients for whom this new insulin is prescribed be instructed in the use of the new 1 ml U-100 syringe. Each calibration of this syringe represents 2 units or 0.02 ml. Every 0.1 ml or 10 unit calibration is marked with corresponding numerals.

When small doses are given or accuracy down to 1 unit is necessary, a 0.35 ml (35 unit) syringe is available in which each calibration represents 0.01 ml or 1 unit.

U-40 and U-80 insulins will continue to be marketed until the use of U-100 is generally accepted.

FDA Drug Bulletin, May 1973

Tardive Dyskinesia Associated with Antipsychotic Drugs

TARDIVE DYSKINESIA, a syndrome characterized by rhythmical involuntary movements, may be associated with the use of phenothiazines and certain other antipsychotic medications. The condition appears in some patients on long-term therapy, sometimes even after it has been discontinued. FDA recommends that the antipsychotic medications be withdrawn immediately if the syndrome appears, and has added the following statement to the ADVERSE REACTIONS section of the package inserts of antipsychotic drugs:

"*Tardive dyskinesia* may appear in some patients on long-term therapy or may occur after drug therapy with phenothiazines and related agents has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Involuntary movements of the extremities sometimes occur. There is no known treatment for tardive dyskinesia; antiparkinsonism agents usually do not alleviate the symptoms. It is advised that all antipsychotic agents be discontinued if the above symptoms appear. If treatment is reinstituted, or dosage of the particular drug increased, or another drug substituted, the syndrome may be masked. It has been suggested that fine vermicular movements of the tongue may be an early sign of the syndrome, and that the full-blown syndrome may not develop if medication is stopped when lingual vermiculation appears."

At times a choice between two evils must be made, as when on the one hand a patient's psychosis worsens without a given antipsychotic drug whereas on the other hand administration of the drug causes severe side effects. Use of the lowest possible dose of the drug adequate to control symptoms appears to be one possible answer. Alternatively, the patient may be given another drug chemically least like that causing the dyskinesia.

The incidence of tardive dyskinesia is not well established. It is rarely seen in acute psychiatric units, even in patients with recurring schizophrenia. But incidence rates of about 20 percent have been reported in older, institutionalized, chronically ill patients. Perhaps 3 percent to 6 percent of patients in a mixed psychiatric population receiving neuroleptics exhibit some aspects of the syndrome at one time or another.

The physician may be able to reduce the risk of producing tardive dyskinesia by:

1. Minimizing the unnecessary use of neuroleptic medication (especially in high doses) in chronically ill patients. Many of the latter can be satisfactorily maintained for long periods without antipsychotic drugs. Drug holidays are advised in patients receiving long-term medication.
2. Discontinuing neuroleptics, if possible, at the first sign of abnormal oral or lingual movements or other possible manifestations of tardive dyskinesia.
3. Observing these precautions carefully in the elderly (females especially) and probably in all patients over age 50.

FDA Drug Bulletin, May 1973

Refer to: Cullen PK Jr: Carcinoid tumors of the colon and rectum (Information). Calif Med 119:89-90, Aug 1973

Carcinoid Tumors of the Colon and Rectum

P. KENT CULLEN, JR., MD
Santa Barbara

IN 1808 MERLING first cited the carcinoid as an appendiceal tumor.[1] Five to ten percent of all carcinoid tumors are located in the colon, with the majority occurring in the cecum.[2,3] This tumor is the most common neoplasm of the appendix and is most often found in this organ.[2,4,5] The tumor is present in approximately 0.3 percent[2] of all appendices, variations depending upon the method of reporting. The literature is not clear on carcinoid tumors of "the colon" as reports are related to the appendix, rectum and colon or the colon exclusive of the rectum.[6-9]

Age and Sex

As with other types of tumors, the incidence of carcinoid is highest in middle and old age. Appendicular carcinoid tumors usually occur at 25 to 30 years.[10] The average age of all patients with rectal carcinoids is 55 years.[7] Thirty-nine years is the mean age of patients with malignant rectal carcinoids.[10]

Considering all carcinoid tumors, there is no apparent difference in the incidence in males and females.[10] However, the incidence of carcinoids of the appendix alone is approximately twice as great in females as in males.[10]

Symptoms

Carcinoids of the appendix are usually incidental findings, but occasionally they cause obstruction and are the direct cause of appendicitis. Carcinoids of the colon tend to be large, and the symptoms are similar to those of carcinoma except that carcinoids have less tendency to ulcerate and bleed.[4] Colonic carcinoids tend to be large, the size correlating well with the high rate of metastasis.[9] Most rectal carcinoids produce few symptoms.[6-8,11] Rectal bleeding, change in bowel habits, varying degrees of obstruction, or signs and symptoms of metastatic carcinoma may be present.

Pathology

A yellow character is often noted on cut section. The tumors are usually submucosal. Ulceration is not common, and necrosis rare.[12]

In tumors of the mid-gut, cytoplasmic granules can be demonstrated by the argentaffin reaction.[13] In lesions of the fore-gut and hind-gut, however, silver staining is variable.[13]

The incidence of metastasis from appendiceal lesions is only 3 percent because so often the appendix is removed routinely before dissemination can occur,[4] but from carcinoid tumors of the cecum and colon it is high.[2,4,9] Size is the best criterion by which to predict the malignant potential of these tumors in the rectum.[6,7] Lesions less than 1 cm in diameter are almost invariably benign, and those larger than 2 cm almost always develop local extension or metastasis. In addition to size, invasion into or beyond the true muscularis is an indication of malignancy. For that reason it is imperative that biopsy specimens be deep enough so that invasion can be seen.[6,7]

The reported incidence of multiple carcinoids of the colon[9] and rectum[7] has varied from 2 to 4.5 percent. For other malignant neoplasms associated with carcinoid tumors of the colon[9] and rectum[7] the range is from 2.5 to 38 percent.[25]

Carcinoid Syndrome

Association of the carcinoid syndrome with appendiceal or colonic carcinoids is unusual.[2] There has been only one report of this syndrome in conjunction with a rectal lesion.[14] Ahlgren et al in 1962 published a case of carcinoid tumor of the rectum with moderate rise in serotonin without association of the carcinoid syndrome, the only case of a secreting carcinoid of the rectum described in the literature.[15] Orloff[7] accepts neither of those reports and presents his case well. Ingestion of serotonin-containing foods, such as bananas, tomatoes, avocados, red plums, walnuts and eggplant,[16] and drugs such as methocarbamol and mephensin carbamate,[17] elevate the urinary 5-hydroxyindoleacetic acid (5-HIAA) levels.

Presented at the Los Angeles County Division American Cancer Society Symposium, Neoplasms of the Colon and Rectum, St. Vincent's Hospital, February 14, 1973.

Reprint requests to: P. K. Cullen, Jr., MD, 230 W. Pueblo, Santa Barbara, CA 93105.

Treatment

The treatment of carcinoid tumors is primarily surgical. When lymphatic permeation[18-20] or tumor at the surgical margin[21] is present, right hemicolectomy is advocated for appendiceal carcinoids. Considering that the prognosis of carcinoids of the appendix is excellent, with only a few deaths reported as directly attributable to the tumor,[22] one must be suspect of retreatment of this lesion regardless of the pathologic findings if the tumor is less than 2 cm in diameter.

In a review of the literature, Berardi[9] noted that the procedure most frequently used for colonic carcinoids was hemicolectomy. Anterior resection is the treatment of choice for sigmoid carcinoids.[9] When a nonresectable tumor was found, palliative colostomy or ileocolostomy was done.[9] In patients with the carcinoid syndrome (widespread metastatic disease) palliative resections to decrease the mass of tumor significantly improved the condition of some patients and prolonged life.[9] As was previously noted, recurrent carcinoids are extremely rare.[23]

Rectal carcinoids less than 2 cm in diameter, without muscle invasion, can be treated by local excision, excisional removal, and fulguration of the bed.[6-8] Larger tumors and those invading the muscle require radical extirpation, usually consisting of an abdominoperineal resection with permanent colostomy.[6-8]

Radiotherapy has proved to be of little value in the treatment of carcinoids except in an occasional case of metastasis to the liver.[24]

Prognosis

The prognosis of carcinoid of the appendix is excellent. Moertel and coworkers[5] reported that in a series of 108 patients traced for more than five years and 83 for more than ten years, there were no recurrences regardless of the degree of local invasion. The same observers reviewed more than a thousand cases in the literature and were able to find only two instances of recurrence.

Approximately one-fourth of all patients with malignant rectal carcinoids die postoperatively or from disease within five years.[7]

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In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

Abbott, Donald Humphrey, Riverside. Died May 27, 1973 in Riverside, aged 64. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1933. Licensed in California in 1933. Doctor Abbott was a member of the Riverside County Medical Association.

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Barden, George A., Salinas. Died May 27, 1973 in Salinas, aged 70. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1942. Licensed in California in 1942. M.D. degree from California College of Medicine, 1962. Doctor Barden was a member of the Monterey County Medical Society.

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Barton, Kenneth M., San Francisco. Died June 11, 1973 in San Francisco, aged 41. Graduate of New York University College of Medicine, New York, 1955. Licensed in California in 1963. Doctor Barton was a member of the San Francisco Medical Society.

⁂

Brower, Joseph Donald, San Bernardino. Died February 3, 1973, aged 41. Graduate of the State University of Iowa College of Medicine, Iowa City, 1956. Licensed in California in 1959. Doctor Brower was a member of the San Bernardino County Medical Society.

⁂

Christie, Frank G. S., Los Angeles. Died May 6, 1973, aged 67. Graduate of University of Toronto Faculty of Medicine, 1932. Licensed in California in 1961. Doctor Christie was a member of the Los Angeles County Medical Association.

⁂

Covington, Campbell H., Selma. Died June 9, 1973, aged 61. Graduate of St. Louis University School of Medicine, 1940. Licensed in California in 1940. Doctor Covington was a member of the Fresno County Medical Society.

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DeLaney, Roy Everette, Jr., Fremont. Died May 28, 1973 in Pleasanton of heart disease, aged 48. Graduate of Hahnemann Medical College and Hospital of Philadelphia, 1948. Licensed in California in 1950. Doctor DeLaney was a member of the Alameda-Contra Costa Medical Association.

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Forbes, Harry Benjamin, Long Beach. Died April 6, 1973, aged 95. Graduate of Marion-Sims College of Medicine, St. Louis, 1898. Licensed in California in 1929. Doctor Forbes was a member of the Los Angeles County Medical Association.

⁂

Fuller, William M., Palos Verdes Peninsula. Died May 30, 1973, aged 46. Graduate of the University of British Columbia Faculty of Medicine, Vancouver, 1954. Licensed in California in 1956. Doctor Fuller was a member of the Los Angeles County Medical Association.

⁂

Gibson, Thomas E., San Francisco. Died June 1, 1973 in Walnut Creek, aged 76. Graduate of the University of California Medical School, Berkeley-San Francisco, 1922. Licensed in California in 1922. Dr. Gibson was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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Graham, Ralph Shaw, Sacramento. Died May 10, 1973 in Mendocino, aged 73. Graduate of Case Western Reserve University School of Medicine, Cleveland, 1925. Licensed in California in 1930. Doctor Graham was a retired member of the Sacramento County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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Hnilo, Joseph M., Arcata. Died June 6, 1973 in Arcata, aged 44. Graduate of Stritch School of Medicine of Loyola University, Chicago, 1952. Licensed in California in 1956. Doctor Hnilo was a member of the Humboldt-Del Norte County Medical Society.

⁂

Jackson, Louis Harris, Santa Monica. Died January 13, 1973 in Santa Monica of carcinoma of the kidney and bladder, aged 90. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, 1915. Licensed in California in 1915. Doctor Jackson was a member of the Los Angeles County Medical Association.

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Leggitt, Roy C., Burbank. Died January 4, 1973 of cerebral vascular accident, aged 79. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1925. Licensed in California in 1925. Doctor Leggitt was a member of the Los Angeles County Medical Association.

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Mannell, Thomas J., San Francisco. Died June 17, 1973 of injuries received in an automobile accident near Bolinas, aged 44. Graduate of the University of Oregon Medical School, Portland, 1956. Licensed in California in 1957. Doctor Mannell was a member of the San Francisco Medical Society.

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Slegel, Lorin, Watsonville. Died June 18, 1973 in Arizona of injuries received in traffic accident, aged 68. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1935. Licensed in California in 1946. Doctor Slegel was a member of the Santa Cruz County Medical Society.

BOOK REVIEWS

California Medicine does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

THE CASE FOR AMERICAN MEDICINE—A Realistic Look at Our Health Care System—Harry Schwartz. David McKay Company, Inc., New York City, 1972. 240 pages, $6.95.

During the past few years American medicine has been under fire from all sides. The health care "crisis" has been a popular theme for the liberal press, congressional critiques and scholarly studies of varying quality. Now an outstanding scholar has found that there is something good about American medicine. Harry Schwartz, an economist and historian with a particular interest in Soviet economy, has now produced a splendid small volume intended to be "a realistic look at our health care system."

Professor Schwartz reviews in depth the doctor shortage, the medical cost explosion, the future of HMO's, and concludes with two chapters on lessons from abroad and policies for the future. His most important message is the need to learn from the past and not to rush blindly into revolutionary changes. Professor Schwartz's critical analysis of the potential economic disaster of Health Maintenance Organizations is of the greatest importance.

This is indeed a sober and sensible view of the accomplishments, failures and faults of the American system. It should be required reading for all health professionals, particularly those who are pressing for drastic and potentially disastrous Federal legislative change.

J. Englebert Dunphy, MD

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THE UPPER CERVICAL SPINE—Regional Anatomy, and Traumatology—A Systematic Radiological Atlas and Textbook—Detlef von Torklus, MD; and Walter Gehle, MD, Orthopaedic Clinic and Outpatient Department, University Hospital, Hamburg; Translator, L. S. Michaelis, MD, Soulbury, England. Grune & Stratton, Inc., 111 Fifth Ave., New York, N.Y. (10003), 1972. 101 pages, 244 illustrations, $15.00.

The contents of this book stem largely from the experience of the authors working in an orthopedic clinic in the University Hospital in Hamburg, Germany. The emphasis throughout this small volume is on the morphology, congenital abnormalities, inflammatory conditions and chronic and degenerative changes that may involve the first few cervical vertebrae. The illustrations for the most part are of excellent quality and are well-marked and annotated. The book is particularly good in the chapters devoted to anomalies and malformations.

The book has many references, both in German and in English, and is well-indexed. It can be heartily recommended as a reference text for those interested in abnormalities involving the upper portion of the cervical spine.

Elliott C. Lasser, MD

* * *

STEROID HORMONES AND BRAIN FUNCTION—UCLA Forum in Medical Sciences—Number 15—Charles H. Sawyer and Roger A. Gorski, Editors. University of California Press, 2223 Fulton Street, Berkeley, Ca. (94720). 400 pages, $30.00.

The UCLA Conference on Steroid Hormones and Brain Function included 31 formal presentations that employed behavioral, neurophysiological and cell biology techniques to attack the problem of whether and how steroids affect brain function. The presentations and discussions leave no doubt that the brain is an important target organ for androgens, estrogens, progesterone and the adrenocortical hormones, and that, difficult as the subject is, real progress is being made in advancing our knowledge of the effects of these hormones on the brain.

The conference was divided into six sections: electrophysiological and behavioral influences of adrenal steroids, electrophysiological correlates of sex steroid actions, perinatal influences of steroids on hypothalamohypophyseal function and sexual behavior, hormones and control of sexual behavior in the adult, steroid feedback and brain pituitary mechanisms and clinical correlates.

One of the more interesting findings that emerged from the conference was the fact that not only corticosteroids, but also estrogens and androgens appear to be able to produce a reversal of spontaneous firing patterns in sensitive neurons. For instance, if the spontaneous rate is high, steroid administration will cause a decrease in rate, and *vice versa*. While it is a long step from observing the reversal of single unit activity by steroids to recognition of the biological effects of the reversal, the apparently global nature of the effect may provide a handle for subsequent research on its biological significance.

An outstanding feature of the volume is the handling of the discussions after the presentations and the summarizing discussions after each section. The editors have managed to leave the spontaneity of the conferees uncut (without wasting space), and in reading these useful interludes between papers, one has the feeling that the conferees themselves found the conference to be very stimulating.

It is extremely unfortunate, on the other hand, that the publishers decided to lump the figures for each presentation at the end of the paper. This decision results in the annoying need for the reader to go back and forth in the book if the point being made is illustrated.

Finally, there were only two papers that used human subjects, and unfortunately one feels that we are still a very long way from clinical application of the current neuroendocrine research.

Mary F. Dallman, PhD
Victor S. Schneider, MD

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INTRODUCTION TO NEUROSCIENCE—Edited by Jeff Minckler, MD, PhD, Director of Laboratories, Eisenhower Medical Center, Palm Desert, California. The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Mo. (63141), 1972. 420 pages with 661 illustrations, $22.50.

With the revolution in medical school curricula over the past few years, it has become fashionable to present all the basic science approaches to the nervous system in a single neuroscience course. This volume edited by, and largely written by, J. Minckler is an attempt to provide a comprehensive text suitable for such a pre-clinical neuroscience course. The emphasis is still overwhelmingly morphological with only two brief chapters devoted to all of neuropharmacology, neurochemistry, and neurophysiology, but the scope is considerably broader than the standard neuroanatomy text. Innovative chapters on neuroradiology, tissue culture, experimental neurobiology, and psychobiology are welcome additions to the usual format. Illustrations and diagrams are used generously, and are generally clear and pertinent. Some criticism may be leveled at the photomicrographs, particularly the electron micrographs, which are ofen poorly reproduced.

In addition to use as a medical school text, this volume will be helpful to students in their clinical years and to neurology residents, but it is too simplified for use as a reference resource by the specialist.

Arthur K. Asbury, MD

Refer to: Firestone FN: Needle lung biopsy, bronchial brushing and mediastinoscopy in management of chest diseases. Calif Med 119:1-5, Sep 1973

California Medicine
THE WESTERN JOURNAL OF MEDICINE

Needle Lung Biopsy, Bronchial Brushing and Mediastinoscopy in Management of Chest Diseases

FREDERICK N. FIRESTONE, MD, *Newport Beach*

Ways to know when not to operate and having guidelines for the extent and direction of intrathoracic operations are recurring needs of thoracic surgeons. History, chest film, pulmonary function tests and bronchoscopy have been useful, but inadequate, solutions to these problems in the past.

Needle lung biopsy, bronchial brushing and mediastinoscopy have been used to supplement these conventional diagnostic methods. The result has been that patients with acid-fast and fungal disease, sarcoidosis, and endobronchial inflammatory disorders have been identified for appropriate medical treatment without thoracotomy. In addition, patients with lung cancer in whom the quality of life or survival cannot be aided by surgical operation have been spared thoracotomy. Where co-existing major, systemic illness increases the risk of operation, these additional diagnostic methods have been used to either eliminate the need for thoracotomy or to limit the operation performed to the minimal procedure permitting a satisfactory surgical result.

Needle lung biopsy, bronchial brushing and mediastinoscopy are safe and they do not add to the cost or length of stay in hospital.

THE CONSCIENTIOUS and resourceful thoracic surgeon is always looking for ways to avoid the morbidity of unnecessary thoracotomy. In addition, he prefers to begin an intrathoracic operation with a well-designed plan for the extent and direction of the procedure. History, x-ray film of the chest, pulmonary function tests and bronchoscopy have been the traditional solutions to these problems. These methods have proved lacking, however, and in recent years needle lung biopsy, bronchial brushing and mediastinoscopy have supplemented conventional diagnostic methods. Our use of these supplementary procedures is illustrated in the following reports of cases.

Needle Lung Biopsy

The Nordenström[1] method of lung biopsy is employed in the x-ray special procedures room with fluoroscopy and television monitor. Disposable 20-gauge spinal or aortography needles are much less traumatic than larger bore needles or a pneumatic drill, yet quite adequate material for cytologic examination can be obtained with them. The incidence of pneumothorax and bleeding has been much less with fine needles.

CASE 1. A 70-year-old construction worker had been a heavy smoker until three years before his present illness. Two months before admission to

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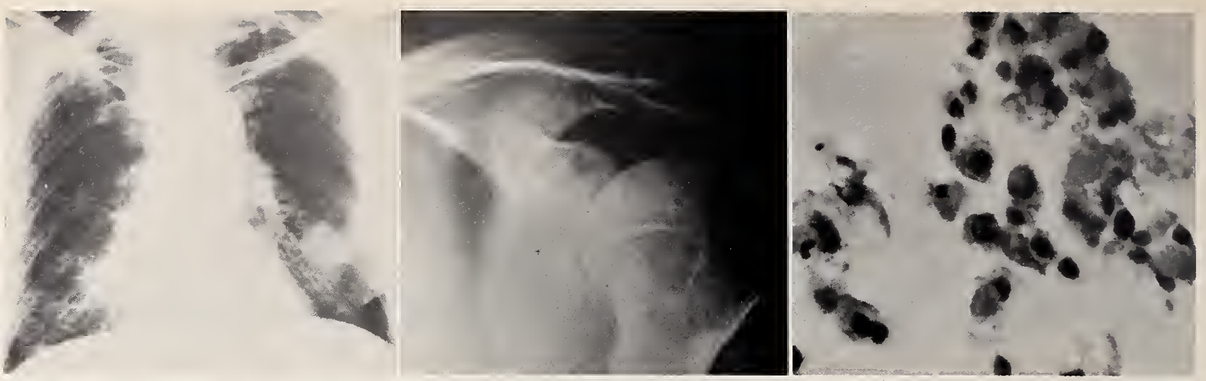

Figure 1.—Left, a 2.0 x 3.5 cm mass is seen on frontal roentgenogram in the left lower lobe. **Center**, considerable destruction of the subglenoid area of the left scapula. **Right**, needle aspirate of lung tumor reveals poorly differentiated squamous cell carcinoma (× 440).

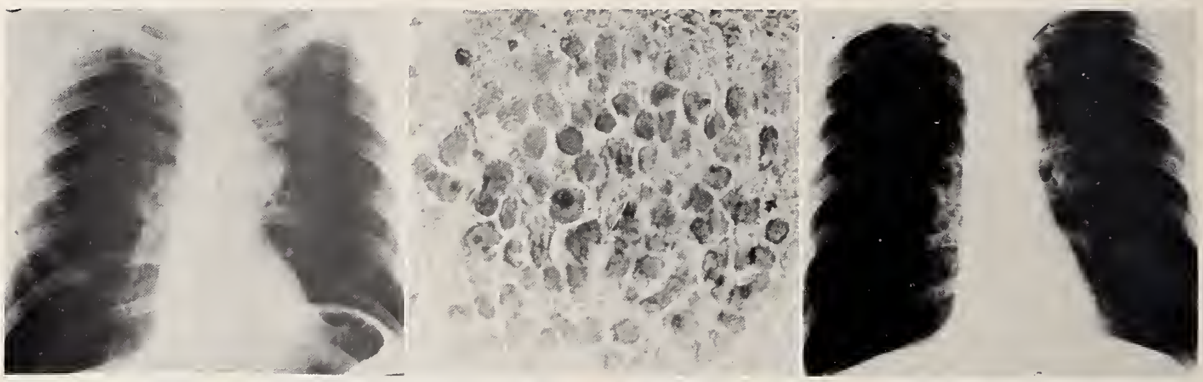

Figure 2.—Left, central left-upper lobe tumor with elevation of the diaphragm. **Center**, needle biopsy specimen of the lesion identified a small cell, undifferentiated carcinoma (× 440). **Right**, response of tumor and diaphragmatic paralysis two months after cobalt therapy.

hospital, he had had a chest cold with cough and left shoulder pain that was relieved by aspirin. A month before admittance he consulted his family physician and a film of the chest (Figure 1) showed a mass in the left lower lobe. The following month he was seen in orthopedic consultation with progressive shoulder pain and a roentgenogram demonstrated an extensive osteolytic lesion of the glenoid area of his left scapula (Figure 1). The patient was then admitted to hospital and bronchoscopy with biopsy and bronchial washings were negative for tumor. There were no palpable scalene lymph nodes. Needle lung biopsy (Figure 1) demonstrated poorly differentiated squamous cell carcinoma. A course of radiotherapy to both the shoulder and lung was given and the patient lived for five months after the onset of the symptoms of metastasis.

Case 2. A 47-year-old marketing manager who smoked two packs of cigarettes daily until a year before he was first seen, consulted a physician when he noted dyspnea on minimal exertion at the altitude of Mexico City. He was found to have moderately advanced emphysema. In the ensuing year he had progressive limitation in activity and loss of weight.

He was seen by us when his voice became hoarse and he noted left shoulder and arm pain. At that time indirect laryngoscopy revealed paralysis of the left vocal cord. An x-ray film of the chest (Figure 2) showed a central lesion of the left upper lobe with distal pneumonitis, in addition to elevation of the diaphragm. The clinical manifestations were consistent with a malignant tumor of the left upper lobe involving the left recurrent laryngeal nerve and the left phrenic nerve. Bronchoscopy and left scalene biopsy were non-diagnostic. On needle lung biopsy a small cell undifferentiated carcinoma was diagnosed (Figure 2). Cobalt irradiation reduced the primary tumor and relieved phrenic nerve paralysis (Figure 2). The patient survived another 11 months free of symptoms until fatal cerebral metastasis developed.

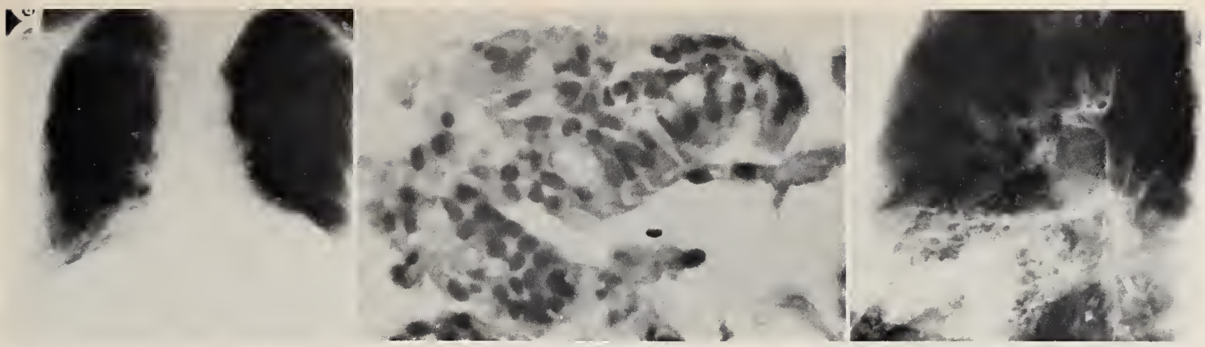

Figure 3.—Left, paracardiac density on the right. **Center,** ciliated respiratory epithelium and inflammatory cells were noted in the bronchial brush specimen (× 440). **Right,** injection of oily Dionosil® under pressure filled the middle and lower lobe bronchi without demonstration of tumor.

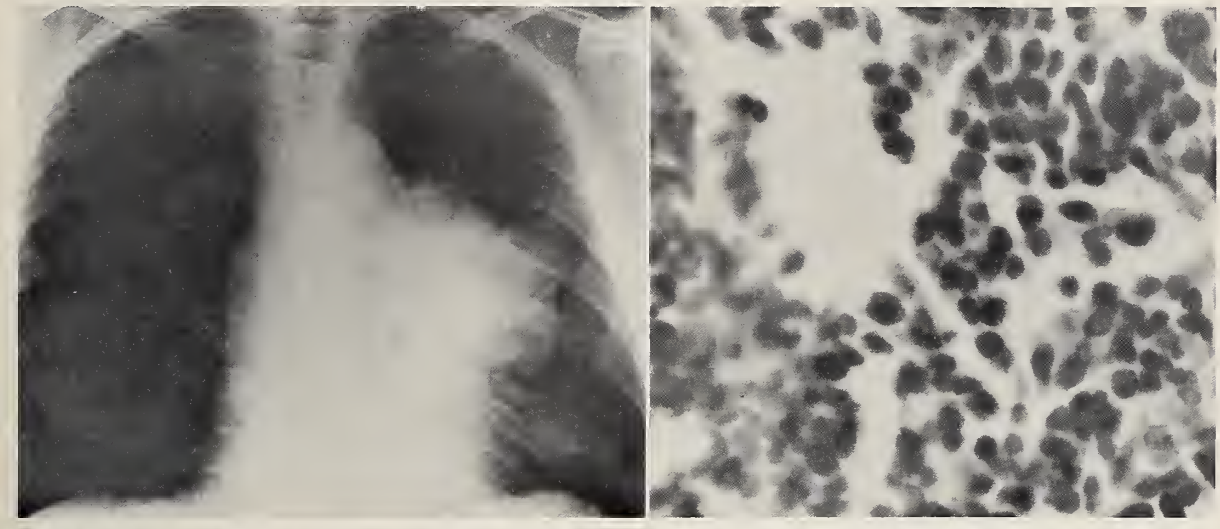

Figure 4.—Left, the left pulmonary hilus is occupied by a massive tumor. **Right,** microscopic examination of left paratracheal lymph node showed a nest of oat cell carcinoma (× 440).

Bronchial Brushing

For bronchial brushing the technique of Zavala and co-workers[2] is used.* After the bronchial brush specimen is obtained, selective bronchography is performed through the guiding catheter for additional information. Recently the glass fiber bronchoscope has been used at our institution and has been found very useful in the examination of mid-lung lesions.

Case 3. A 70-year-old woman had a febrile illness and cough lasting for one week, and an x-ray film of the chest taken during the acute illness was interpreted as showing right middle lobe atelectasis. Four weeks later, films of the chest showed persistent atelectasis in the medial segment of the right middle lobe (Figure 3). Bronchoscopy showed acute endobronchitis, and diagnostic and therapeutic washings of the right middle and lower lobes did not change the radiographic appearance of the lungs. Bronchial brushing produced a plug from the involved bronchus (Figure 3). Selective bronchograms were performed at the same time (Figure 3). The patient subsequently had relief of atelectasis, and cytologic studies of the sputum were negative for abnormal cells.

Mediastinoscopy

For mediastinoscopy the Carlens mediastinoscope is employed, and the method is that described by Palva.[3]

Case 4. The patient, a 44-year-old retired serviceman, had begun work as a postal employee a year before examination. Seven months before he was seen by us, trigeminal neuralgia developed on the left side. A month before examination, he

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*Bronchial brushing instruments used are those of U.S. Catheter & Instrument Corp., Box 787, Glen Falls, New York.

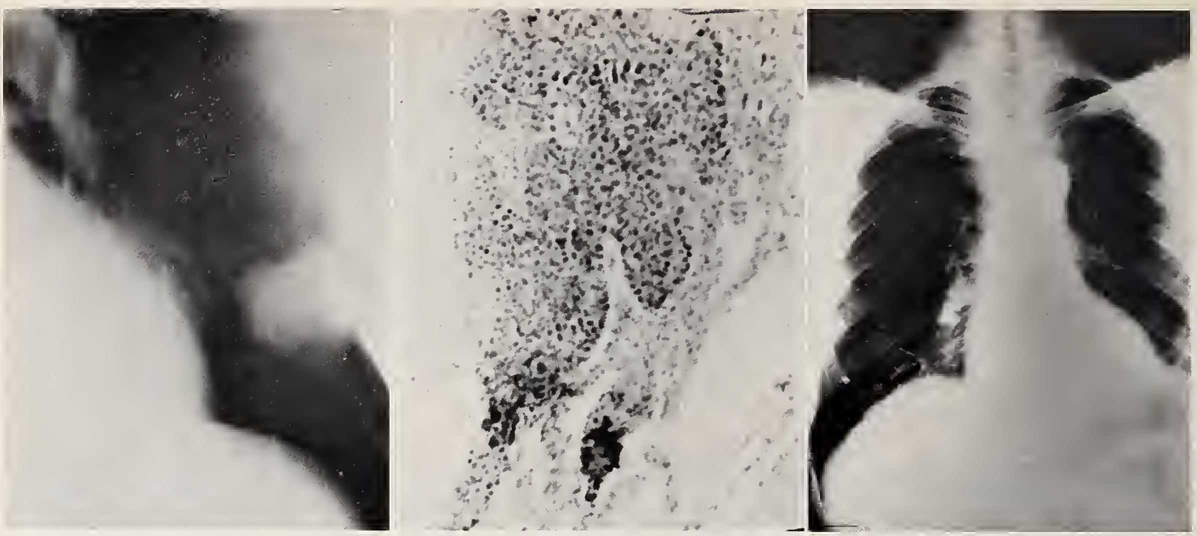

Figure 5.—Left, a lobulated, non-calcified tumor of the lower lobe was noted on tomography. **Center,** a poorly differentiated squamous cell carcinoma invades the lung (× 100). **Right,** x-ray film after lobectomy shows inactive granulomatous disease without recurring tumor.

began to have pleuritic pain at the front of the left side of the chest and pain in the left deltoid area. He had smoked a pack and a half of cigarettes daily all his adult life and had had pneumonia 24 years before the present illness. An x-ray film of the chest (Figure 4) revealed a large left hilar mass. Bronchoscopy showed a narrowing and fixation of the left main bronchus, but bronchial biopsy and washings were negative. Mediastinoscopy showed abnormal high paratracheal lymph nodes on the left, and on histologic examination (Figure 4) oat cell carcinoma was diagnosed. The primary tumor diminished greatly in size with cobalt irradiation, but phrenic nerve paralysis developed and the disease spread. The patient died two months later.

CASE 5. The patient, a 61-year-old man, had worked in southern Illinois soft coal mines for 22 years and had been a two packs a day cigarette smoker. His brother had died of silicosis. Injuries in two major mine accidents had caused deformity of his left arm and amputation of the left leg below the knee. A year before examination by us he had been admitted to the hospital with myocardial infarction and cardiac arrest. Following successful resuscitation and convalescence, he returned to his previous level of activity. He was readmitted to the hospital with an abnormal chest film demonstrating old granulomatous changes and a new mass, not demonstrated in the films a year previously, in the left lower lobe. Laminograms were highly suggestive of a non-calcified tumor (Figure 5). Bronchoscopy and bronchial washings were negative. Mediastinoscopy produced small tracheobronchial nodes showing anthrocosis only. Left lower lobectomy was performed and a poorly differentiated squamous cell carcinoma (Figure 5) was found in the specimen. Bronchial margins were clear and no lymph node metastasis was present. At last report the patient was symptom-free. A chest film 18 months after the operation is shown in Figure 5.

CASE 6. A 28-year-old housewife was admitted to hospital with a three-month history of progressive breathlessness and non-productive cough. She had worked in a factory which made cellucotton tissues and she said that a silicone spray used to lubricate the machinery there was highly irritating to her lungs. She had been admitted to the hospital one month earlier during this illness, which from an x-ray film of the chest and the clinical course had been diagnosed as viral pneumonia. Treatment with antibiotics and inhalation therapy had brought about clinical improvement. She was readmitted to the hospital when her symptoms became much worse. Her vital capacity was 30 percent of normal and her maximum ventilatory volume only 40 percent of predicted. A roentgenogram at that time (Figure 6) demonstrated extensive consolidated processes in both lungs and there was also a suggestion of mediastinal widening. Mediastinoscopy was performed and a succulent lymph node was removed from the left tracheo-bronchial area. On microscopic examina-

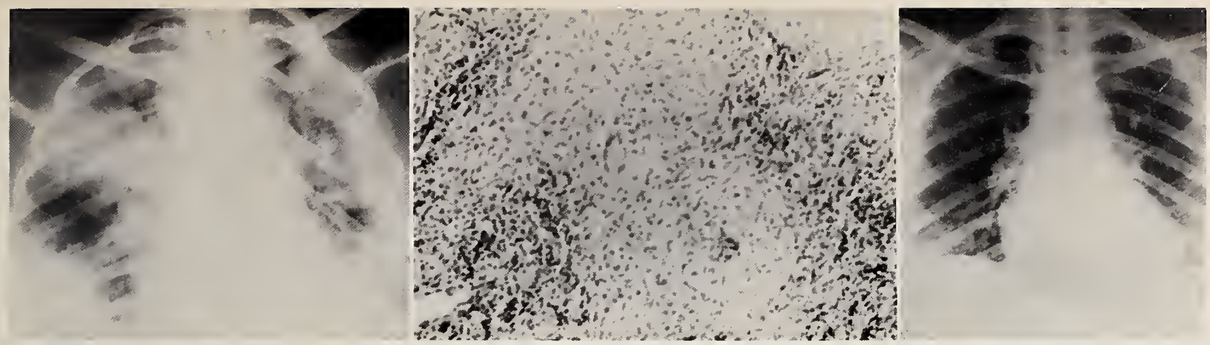

Figure 6.—Left, roentgenogram showing bilateral pulmonary infiltrates and superior mediastinal widening. **Center,** granulomata without caseation containing many Langhans giant cells in a mediastinal lymph node (× 100). **Right,** clearing of the pulmonary parenchyma following steroid therapy.

tion it was found to be filled with non-caseating granulomata and Langhans giant cells (Figure 6). A diagnosis of sarcoidosis was made, and steroid therapy brought about dramatic resolution of the proliferative changes in the lungs (Figure 6). The patient resumed normal household activities. She is currently in remission without steroid therapy.

Discussion

Infections of the lungs with acid-fast bacilli or fungus, sarcoidosis and endobronchial inflammatory disorders are best treated by drugs and pulmonary medical management. Needle biopsy, bronchial brushing and mediastinoscopy have been found extremely helpful for making the diagnosis in such cases.

Experience has provided us with certain guidelines for the selection of the correct diagnostic procedure. Needle biopsy is ideal for identifying solitary pulmonary nodules. With this safe diagnostic aid, a policy of observation of solitary pulmonary nodules is no longer warranted. Early needle biopsy of malignant chest tumors results in earlier operation and increased survival. When the lesion under question is at the level of the secondary or tertiary bronchi, bronchial brushing or the fiberoptic bronchoscope should be employed. Mediastinoscopy is best applied in the investigation of mediastinal tumors or when biopsy of paratracheal, tracheobronchial or subcarinal lymph nodes is necessary. Kirschner[4] schedules patients with suspected tumors for consecutive bronchoscopy, mediastinoscopy and thoracotomy under one anesthetic. I prefer scheduling the bronchoscopy and mediastinoscopy on separate days, since frozen section diagnosis often is incomplete and one must await permanent histologic examination before proceeding to thoracotomy.

Resection of lung cancer should be limited to patients in whom the quality of life can be enhanced or survival prolonged by the operation. I believe thoracotomy is contraindicated in patients with: (1) oat cell carcinoma at any stage, (2) other lung cancers with bilateral or high paratracheal lymph node spread, (3) a clinical diagnosis of primary lung tumor and remote metastasis without histological diagnosis, or (4) pulmonary metastasis unless the primary tumor is identified and controlled. Application of needle lung biopsy, brush biopsy or mediastinoscopy allows identification of such patients and treatment with chemotherapy or irradiation without thoracotomy. A positive benefit in this diagnostic program has been a pronounced increase in the resectability rate of those patients in whom thoracotomy is performed. Where co-existing major systemic illness increases the risk of operation, these additional diagnostic methods have been used either to eliminate thoracotomy or to limit operation to the minimal procedure that will permit a satisfactory surgical result.

Needle lung biopsy, bronchial brushing and mediastinoscopy are safe and they do not add to the cost or length of stay in hospital. They should be added to the armamentarium of any physician dealing with thoracic diseases.

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Refer to: Glynn KP, Alazraki NP, Waltz TA: Coccidioidal meningitis—Intrathecal treatment with hyperbaric amphotericin B. Calif Med 119:6-9, Sep 1973

Coccidioidal Meningitis

INTRATHECAL TREATMENT WITH HYPERBARIC AMPHOTERICIN B

KEVIN P. GLYNN, MD, NAOMI P. ALAZRAKI, MD, *and* THOMAS A. WALTZ, MD, *San Diego*

UNTREATED COCCIDIOIDAL MENINGITIS is uniformly fatal. Winn,[1,2] Einstein,[3] and Caudill[4] have reported good results using suppressive doses of amphotericin B administered intravenously, and, most important, have advocated intrathecal cisternal injection, or ventricular injection through an Ommaya reservoir, to achieve high cerebrospinal fluid concentrations of the drug.

Administration of anesthetics into the subarachnoid space in hyperbaric solutions of glucose is a widely used technique,[5] and recently an application of this method has been described for hyperbaric cisternography.[6] It was reasoned that administering amphotericin B in 10 percent glucose solution, via the lumbar route, with immediate lowering of the patient into the Trendelenberg position might favor migration of the drug to the occipital region and make a simpler and safer way to administer therapy, obviating the potential hazards of repeated cisternal puncture or prolonged reservoir placement.

The successful use of this method in a patient with coccidioidal meningitis, with two years of follow-up, prompts this report.

Methods

A 50 mg vial of amphotericin B was diluted with sterile water containing no preservative to give a concentration of 5 mg per ml. A volume of 0.05 to 0.1 ml (0.25 to 0.5 mg) was withdrawn and diluted with 5 ml of 10 percent glucose in water, to which 25 mg (0.5 ml) of hydrocortisone succinate was added, making a total volume for injection of 5.5 to 6 ml.

A lumbar puncture was performed with a 20-gauge spinal needle at the third to fourth or fourth to fifth lumbar interspace, with removal of 5 or 6 ml of cerebrospinal fluid for analysis. Twenty-five mg (0.5 ml) of hydrocortisone was injected, followed by the hyperbaric amphotericin B solution described above. As the injection was being completed, the table was tilted to an angle 30° below horizontal, bringing the patient's head to a position below the spinal needle. An additional 0.5 ml of 10 percent glucose in water was injected after the amphotericin B mixture, and the needle withdrawn. The patient was placed in the supine position, remained with his head down for 45 minutes, and then went back to his room or home.

Simultaneous administration of ^{131}I-serum albumin with the hyperbaric amphotericin B solution was performed on two occasions, enabling scintillation camera images of the cephalad migration of the ^{131}I to be obtained. The scintiphotos documented the rate of spinal clearance of the hyperbaric bolus and its arrival at the basal cisterns. For comparison, images were made after the lumbar intrathecal injection of isobaric ^{131}I-serum albumin, following the spinal clearance with conventional cisternographic techniques. Cisternal puncture for amphotericin B analysis was not performed on the patient presented, because of the good clinical response to the lumbar hyperbaric injections.

After the injection the patient occasionally complained of low back pain and mild headache, which would sometimes last four to five hours, in which case he would take one or two capsules of D-propoxyphene with aspirin compound (65 mg) with satisfactory relief.

Submitted February 21, 1973.

Reprint requests to: K. P. Glynn, MD, 4094 Fourth Avenue, San Diego, CA 92103.

The localization of coccidioidal meningitis in the basilar regions, with resultant hydrocephalus and uniformly fatal outcome, has necessitated intrathecal injection of amphotericin B via cisternal puncture or subcutaneous ventricular reservoir for successful therapy. A simpler form of treatment is described here, whereby amphotericin B diluted in 10 percent glucose solution is injected via lumbar puncture, and delivered to the base of the skull by tilting the patient to a head-down position. A simultaneously performed hyperbaric cisternogram with ^{131}*I-serum albumin has demonstrated satisfactory migration of the injected bolus to the occiput. This method of administration resulted in successful suppressive treatment of one patient, including two years of follow-up without serious sequelae or relapse.*

Report of a Case

A 70-year-old retired machinist was admitted to hospital on 20 February 1971 with a two-day history of headache and photophobia. Six months before, he had had a dry cough, low grade fever, malaise, and night sweats. A month before admission he began to notice steady pain in the left side of the chest. He consulted a physician, who noted an infiltrate in the left upper lobe. On the basis of a 15 mm reaction to 1:100 coccidioidin, and the presence of serum precipitins, a diagnosis of coccidioidal pneumonitis was made. The patient had been a lifelong resident of San Diego County. Except for insertion of a prosthetic left femoral head in 1969 for osteoarthritis of the hip, his past history was unremarkable.

Except for temperature of 37.8°C (100°F) and deformity and decreased motion of the left hip, results of physical examination were within normal limits.

The hematocrit was 30 percent, hemoglobin content was 12 grams per 100 ml and sedimentation rate was 67 mm per hour. The white cell count was 7,600 per cu mm with a normal differential. Skull films and brain scan were normal; an echoencephalogram showed no shift of midline structures. Serum coccidioidal precipitins were present at a dilution of 1:10, and the complement-fixation titer was 1:32. Lumbar puncture showed an opening pressure of 180 mm of water with clear spinal fluid. There were 225 white cells per cu mm, of which 50 percent were neutrophiles and 50 percent mononuclear forms. Protein content was 84 mg and sugar content 50 mg per 100 ml. (Simultaneous blood sugar was 112 mg per 100 ml). The cerebrospinal fluid contained complement-fixing antibodies to C. immitis at a titer of 1:16, and the organism was subsequently cultured from it.

Therapy consisting of combined intravenous and intrathecal amphotericin B was started. After an initial dose of 0.25 mg of amphotericin B given intracisternally, lumbar intrathecal administration in hyperbaric glucose solution was continued for six weeks, using a schedule of 0.25 mg every other day, by which time the patient had received 960 mg of amphotericin B intravenously and 4.15 mg intrathecally. The fever and headache subsided, and the spinal fluid white cell count fell to 75 per cu mm. The protein content decreased to 60 mg and the glucose level remained at 53 mg per 100 ml.

From April 1971 to the present the patient has been treated as an outpatient by the lumbar hyperbaric technique of intrathecal amphotericin B administration, with gradually increasing time intervals between injections. Current therapy is 0.3 mg of amphotericin B intrathecally every four weeks. Transient neck soreness and low back and leg pain have occurred after the injections, suggesting arachnoidal reaction. Currently, the patient's cerebrospinal fluid pressure is 30 mm of water, the fluid white cell count is 4 per cu mm, protein content 42 mg and glucose content 58 mg per 100 ml. (Blood sugar is 94 mg per 100 ml.) The complement-fixing antibody has disappeared from the cerebrospinal fluid and the serum titer has fallen to 1:8. The skin no longer reacts to 1:100 coccidioidin, but there is a 17 mm reaction to 1:10 dilution of antigen. A film of the chest

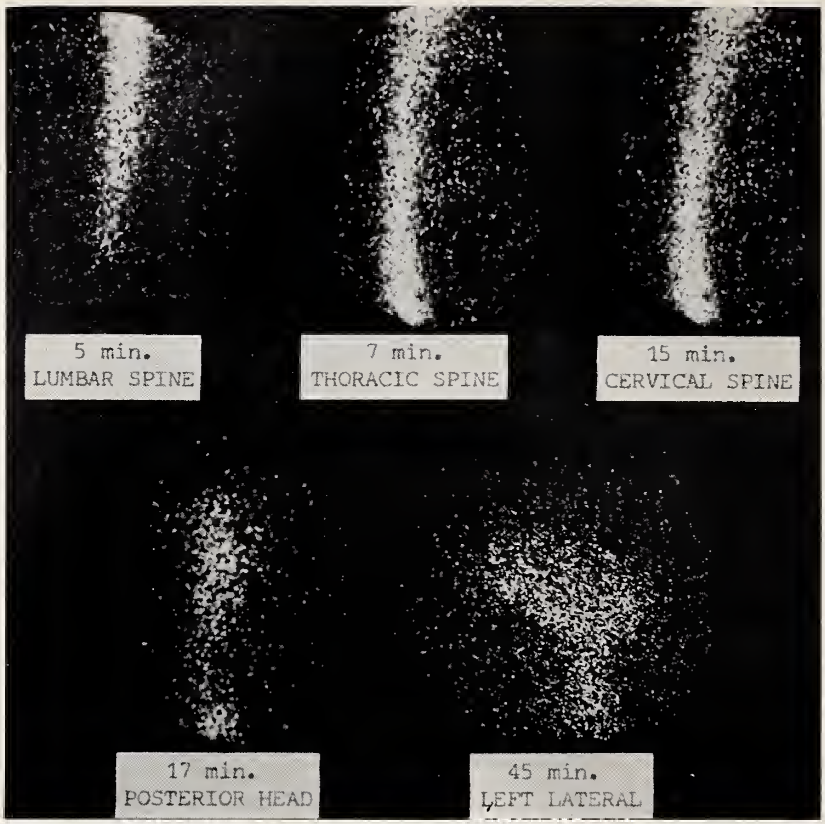

Figure 1.—Hyperbaric cisternogram: Radioactivity clears rapidly from the lumbar injection site 5 minutes after injection, migrates cephalad to the thoracic and cervical spine, and is identified in the region of the basal cisterns 17 and 45 minutes after injection.

shows only a small linear scar remaining in the anterior segment of the left upper lobe.

Results

Figure 1 shows the scintiphotos obtained following imaging with the scintillation camera over the spine and the head of the patient when the lumbar hyperbaric technique was used. The hyperbaric amphotericin B-radiopharmaceutical solution was injected at the fourth to fifth lumbar interspace with the patient in a 30° Trendelenberg position. Radioactivity cleared from the lumbar injection site rapidly so that five minutes after injection relatively little activity was left in the lumbar region, and after 17 minutes there was activity in the basal cisterns.

Figure 2 shows scintiphotos demonstrating an impressively slower disappearance of the nonhyperbaric radiopharmaceutical from the lumbar injection site than was shown in Figure 1. The isobaric ^{131}I-albumin injected with the patient lying flat was concentrated at the lumbar level 20 minutes after injection. After 30 minutes, the activity had not yet progressed cephalad beyond the thoracic spine. At four and a half hours, enough activity was seen in the basal cisterns to obtain the scintiphoto shown.

Discussion

Because of the tendency for coccidioidal meningitis to localize to the basal regions of the brain,[7] with resultant hydrocephalus, a means has been needed to achieve maximum concentration of amphotericin B in this area. Winn[1] emphasized that the cisternal route is the preferred method of treating coccidioidal meningitis. Repeated cisternal punctures are relatively safe in the hands of experienced personnel, but not for the occasional therapist. Insertion of an Ommaya reservoir has been life-saving in selected patients with ventricular infection,[8] but there has been a significant incidence of complications.[9] A simpler and safer method of administration would be desirable.

The satisfactory clinical response obtained in this case suggests that the amphotericin B did migrate to the basilar regions of the skull along with the hyperbaric glucose and iodinated albumin, though this has not been proved directly in this patient. Hyperbaric glucose solutions of anesthetic agents have been utilized successfully, the injected material passing as a bolus with gravity.[5] The patient presented in this report had low back and mild occipital pain after injection, most likely as a result of irritation from the amphotericin B, which is often the limiting factor in intrathecal ad-

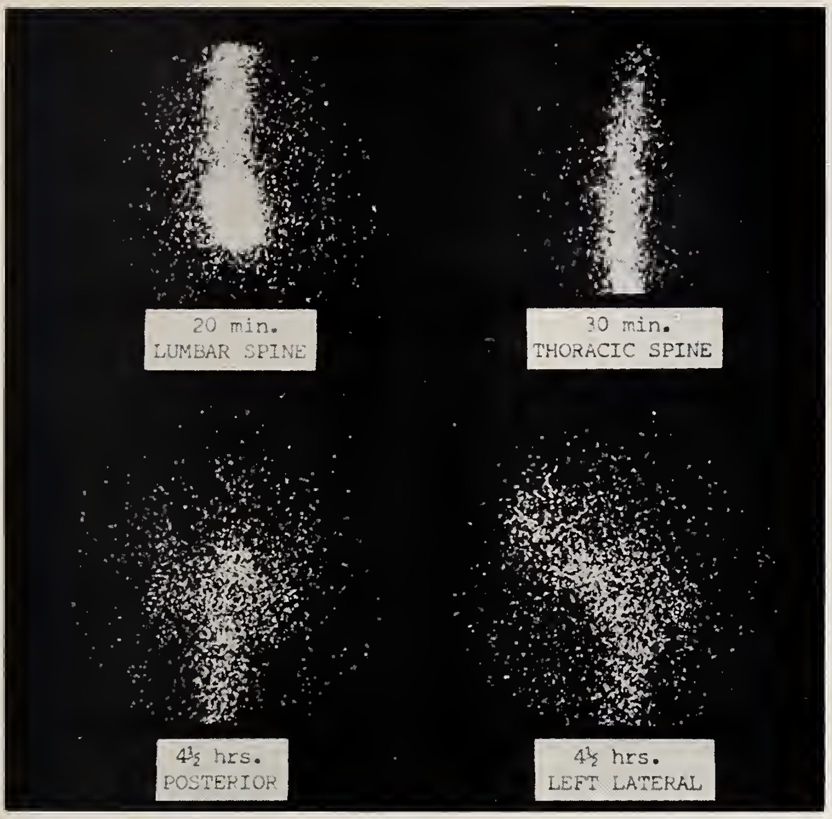

Figure 2.—Non-hyperbaric cisternogram: Radioactivity clears slowly from the lumbar injection site, with scintiphotos demonstrating retention at 20 minutes; by 30 minutes there is still none above the thoracic spine. Four and one-half hours after injection the radiopharmaceutical is in the basal cisterns.

ministration of the drug.[2] To avert this problem, 25 mg of hydrocortisone was injected intraspinally before each dose of amphotericin B, as suggested by Winn,[2] and 25 mg was mixed with the antifungal agent, following the method of Einstein.[3]

The scintiphotos showing the movement of the ^{131}I-albumin in the subarachnoid space (Figures 1 and 2) strongly suggest that the hyperbaric technique facilitates a significantly more rapid and efficient migration of injected material out of the lumbar reigon, cephalad to the basal cisterns. Additional supporting evidence in animals has been given in a report[10] describing the behavior of hyperbaric radiopharmaceutical solutions injected into the lumbar intrathecal confines.

This leaves open the question as to whether lumbar intrathecal injection alone would have produced as good a result. Winn[1] reported the results of treatment of 31 patients with combined intravenous and intrathecal amphotericin B. Four of five patients in that series who received only intravenous and lumbar intrathecal injections died. The one survivor was a five-year-old child. Caudill, Smith and Reinarz[4] also reported successful treatment of one patient solely by intravenous and lumbar intrathecal therapy. Therefore it is likely that, to achieve a good therapeutic level, and to avoid lumbar arachnoiditis, a special effort is needed to bring sufficient amphotericin B from the lumbar to the basilar area.

In conclusion, it appears that amphotericin B administered intrathecally in a hyperbaric glucose via lumbar puncture migrates to the occipital region. This method provides an easy and effective method of treating coccidioidal meningitis, and deserves application in other patients with this disease.

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Refer to: Keane JR: Cisternal puncture complications—Treatment of coccidioidal meningitis with amphotericin B. Calif Med 119:10-15, Sep 1973

Cisternal Puncture Complications

Treatment of Coccidioidal Meningitis with Amphotericin B

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Of two patients who had acute neurologic damage from cisternal punctures, one died 17 hours following a tap which produced major subarachnoid hemorrhage, the other patient recovered from probable brain stem infarction associated with cisterna magna amphotericin injection.

Subarachnoid hemorrhage is the commonest major complication of cisternal puncture, with at least 30 reported fatalities. Other serious complications result from direct puncture of brain substance.

Cisternal puncture is not an appropriate alternative to a difficult lumbar puncture, and indications for its use are limited. The occasional required cisternal tap should be performed only by persons carefully trained in the technique, preferably utilizing fluoroscopic guidance, and only where neurosurgical assistance is readily available.

Post-puncture subarachnoid hemorrhage accompanied by progressive obtundation requires emergency evaluation and consideration of posterior fossa decompression.

INTRATHECAL AMPHOTERICIN B TREATMENT of coccidioidal meningitis has greatly increased the number of cisternal punctures performed in California and Arizona.

Ayer and other clinicians performing early percutaneous punctures of the cisterna magna stressed the importance of preliminary practice on cadavers and the need for exacting technique to avoid possibly disastrous complications, but recent descriptions are more inclined to stress patient acceptance, technical ease, and a low incidence of post-puncture headache.

The following two case reports illustrate the hazards of cisternal puncture.

CASE 1. A 31-year-old man with chronic renal failure secondary to glomerulonephritis had acute onset of severe low back pain radiating down both legs and increasing with any movement of the

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back. When seen the next day for a regular hemodialysis appointment, he had excruciating low back pain and body temperature of 39.4°C (103°F). He was admitted for evaluation.

On admission he had lower lumbar and sacral tenderness with paraspinal muscle spasm, straight leg raising limited to 30° bilaterally, and moderate nuchal rigidity. The abdomen was soft and without masses. On neurologic examination there were no abnormalities except for a previously documented chronic neuropathy with absence of lower extremity reflexes. The white blood cell count, serum amylase and liver function tests were within normal limits. Serum creatinine was 12.2 mg per 100 ml. Lumbosacral spine x-ray studies and tomograms were normal. Pain and fever persisted, and when staphylococcus aureus grew from the blood cultures, treatment with cephalothin and then amipicillin was instituted.

On the fourth hospital day a neurological consultant suggested the possibility of spinal epidural abscess. An emergency myelogram was performed through a cisternal puncture to avoid possible cerebrospinal fluid contamination. An uneventful myelogram revealed a complete block at the fourth lumbar level, but subsequent laminectomy revealed a fibrous extradural constricting band at the fourth-to-fifth interspace without evidence of infection.

The cerebrospinal fluid at the time of myelography showed 170 white blood cells and 30 red blood cells, protein content of 124 mg and glucose of 74 mg per 100 ml. Postoperatively the back pain and nuchal rigidity persisted, but no new neurologic signs developed. The temperature continued to spike and blood cultures remained positive, but no definite source of infection was found.

Eight days after operation a cisternal tap was performed to re-evaluate the cerebrospinal fluid. The puncture was performed without difficulty but midway through the fluid collection a few drops of blood were noted on readjustment of the position of the needle. (Microscopic examination showed 2,200 red blood cells, five neutrophils, and one mononuclear cell.) Shortly after the cisternal puncture, the patient complained of severe neck pain and nausea but no changes were noted on neurologic examination. Seven hours after the procedure the patient complained of "anxiety" in addition to continuing nausea and neck pain. Respirations were noted to be rapid but the pulse was 80 and regular, the blood pressure was 170/80 mm of mercury, and again no localizing neurological deficits were noted. Three hours later stupor developed and the patient rapidly became comatose, with loss of all brain stem reflexes. Cardiac arrest occurred 17 hours after the cisternal puncture.

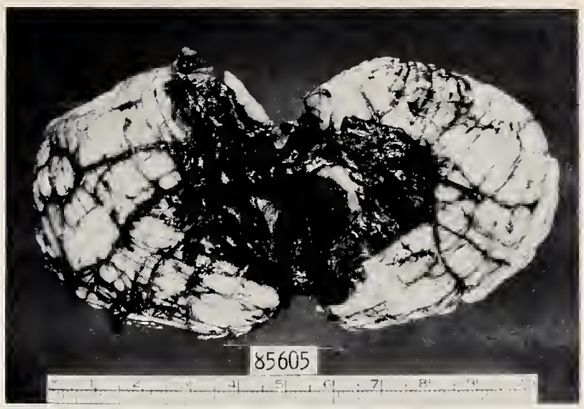

Figure 1.—Subarachnoid hemorrhage filling the cisterna magna (Case 1).

Postmortem examination revealed subarachnoid blood filling the cisterna magna, diffusely coating the brain stem (Figure 1), and extending into the fourth and third ventricles. The site of the bleeding could not be identified. The spinal cord was normal, with no evidence of epidural abscess. Indeed, no evidence of infection anywhere in the body was discovered, although the vertebral bodies were not specifically examined.

Comment

A major subarachnoid hemorrhage followed cisternal puncture, with brain stem decompensation occurring ten hours later. The absence of localized neurologic signs engendered a false sense of security.

The patient's underlying meningeal reaction may have been secondary to occult lumbar vertebral osteomyelitis, but the possibility of uremic meningitis[1] unrelated to the sepsis cannot be excluded.

CASE 2. A 45-year-old woman was admitted in acute distress following a cisternal injection of amphotericin.

Nine months earlier the diagnosis of coccidioidomycosis had been established by skin biopsy when she presented with a six-month history of progressive verrucous back lesions and elephantiasis of the left lower extremity. The only neurologic complaint at that time was of mild headache but the coccidioidomycosis complement fixation titer of the

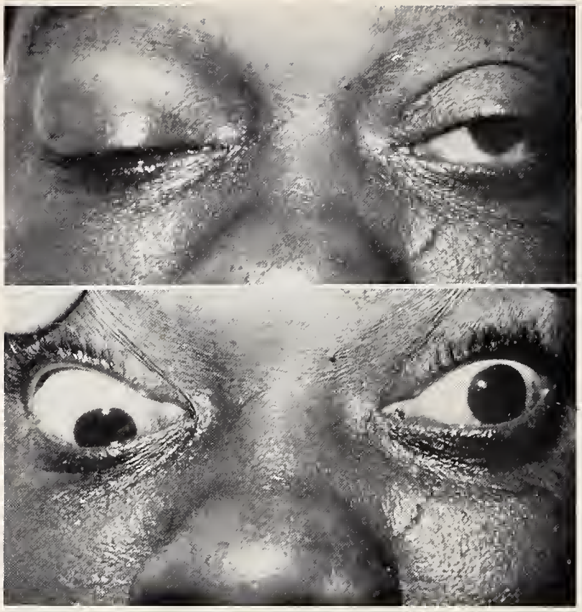

Figure 2.—Ptosis and skew deviation six hours after cisternal injection (Case 2).

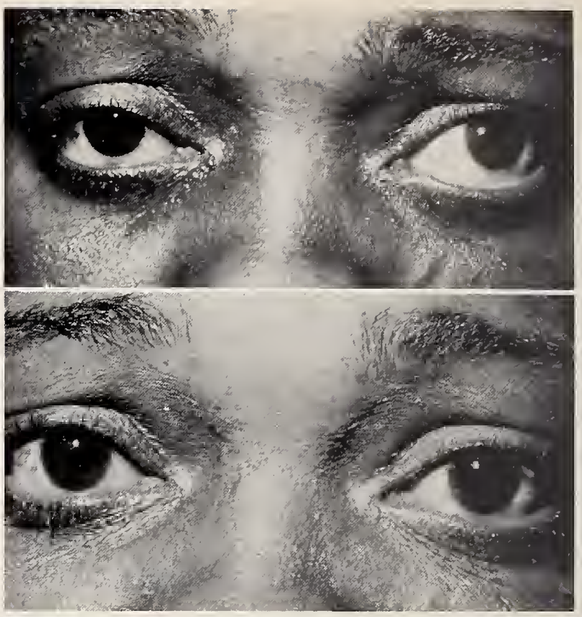

Figure 3.—**Upper,** 24 hours after injection (Case 2). **Lower,** two months after injection.

cerebrospinal fluid was 1 plus in a dilution of 1:16 and 4 plus in a dilution of 1:8.

Intravenous and intrathecal amphotericin B therapy was begun, but the initial biweekly lumbar subarachnoid injections of 0.10 mg soon proved too uncomfortable because of back pain, and after six injections an attempt was made to place an indwelling Ommaya reservoir-shunt to facilitate therapy. The attempt at ventricular cannulation was unsuccessful and resulted in a moderate left hemiparesis which slowly cleared over the next several months.

The intrathecal injections were then given cisternally and the patient received biweekly injections of 0.25 mg of amphotericin intracisternally and 50 mg intravenously. A total of 2,450 mg intravenously and 10 mg intrathecally was given without incident. The cerebrospinal fluid titer remained 4 plus positive at a 1:4 dilution, but no neurologic symptoms or signs developed.

On the thirty-seventh cisternal puncture blood appeared on the needle but the patient had no apparent ill effects. Immediately following the thirty-ninth injection of 0.25 mg of amphotericin with 20 mg of methyprednisolone acetate she complained of excruciating headache with severe nausea. After reclining for several hours, she attempted to go home but collapsed on arising. She regained consciousness after several minutes but progressive lethargy, dysarthria and right sided weakness followed and she was transferred to the neurology service.

On examination six hours after cisternal puncture the patient was stuporous and had severe dysarthria. The blood pressure was 150/80 mm of mercury, the pulse was 100, respirations 36, and the temperature 38.3°C (101°F). Although lethargic, she was well oriented and able to carry out commands. She could make sounds but few intelligible words even though her swallowing and tongue motion appeared normal. Bilateral ptosis, much greater on the right, was apparent, and a pronounced right hypotropic ocular skew deviation was present (Figure 2). The pupils were 5 mm, equal and reactive. There was mild right facial weakness and decided weakness of the right extremities, with hyperactive reflexes on the right side and a right extensor plantar response. Hypesthesia on the right side, including the face, and mild intention tremor of the left extremities were present.

Cerebrospinal fluid taken at the time of the cisternal tap showed 8 white blood cells and 24 red blood cells, while a lumbar puncture four hours after cisternal injection revealed a pressure of 270 mm of water, 800 white blood cells with 10 percent neutrophils, 70 red blood cells, protein content of 129 mg and glucose of 35 mg per 100 ml.

All the neurologic signs progressively cleared and on readmission two months later she had only minimal right ptosis (Figure 3), mild dysarthria and mild right hemiparesis with a nearly normal gait. Pneumonencephalography and RISA cisternography with radioiodinated serum albumin demonstrated normal ventricular size without evidence of cerebrospinal fluid obstruction, and intrathecal amphotericin was not resumed.

Comment

The difficulties associated with intrathecal amphotericin administration are well illustrated by this case. Injection by lumbar puncture led to the expected back pain and radiculitis. The attempted change to ventricular catheter administration produced hemiparesis. The thirty-ninth cisternal injection was followed by acute brain stem damage.

The rapid onset of severe nausea and the subsequent anarthria suggest a direct medullary puncture, but the neurologic signs indicate brain stem damage that is bilateral and present at several levels. When the delayed progression is considered, it seems most likely that the chemical meningitis, documented on lumbar puncture, produced sufficient vasospasm which caused scattered brain stem infarcts.

The absence of blood on lumbar puncture dictated conservative therapy.

Discussion

Percutaneous puncture of the cisterna magna had been performed in animal studies for several years before Ayer published the first clinical series in 1920.[2,3] In a report of 43 punctures in 20 patients, he stressed relative safety but emphasized the need for preliminary practice of technique on cadavers.[3] There were no complications in his patients, but injury to the medulla occurred in ten of 1,186 preliminary punctures done on cats.[2]

In its early days, cisternal puncture was widely used in the diagnosis and treatment of lues, in serum treatment of meningitis, and in subarachnoid perfusion. Relatively few complications were reported; probably most went unreported. It seems generally agreed, however, that the test was relatively safe in very experienced hands.

Two major types of cisternal puncture complications are reported—subarachnoid hemorrhage and direct puncture of brain tissue. Aside from those attributed to grossly improper technique, most incidents occur in patients with anatomic variations of the posterior fossa, including large midline posterior inferior cerebellar artery branches, congenitally small posterior fossas, and inferior displacements of the brain stem and cerebellar tonsils.

In cases involving subarachnoid hemorrhage, the patients usually present with immediate headache, agitation, and stiff neck. Within minutes to several hours, or rarely after several days, progressive obtundation and various brain stem signs occur. In the cases examined at operation or autopsy, the hemorrhage fills the cisterna magna, acting as an acute mass to compress the brain stem directly and obstruct fourth ventricular outflow. Relief of this mass effect by posterior fossa decompression has seemed of value in the limited number of surgical cases.

Direct puncture damage usually involves the medulla, but occasionally the cerebellar tonsils or the pons are damaged. Symptoms of coughing, vomiting, generalized weakness, "electric" sensations of one side of the face or body, and respiratory dysfunction typically occur immediately. Fewer deaths have been related to direct puncture injury than to subarachnoid hemorrhage.

The first report of fatal complication was published by Nonne[4] in 1924. The patient, 79 years of age, died of subarachnoid hemorrhage from puncture of a tortuous arterosclerotic posterior inferior cerebellar artery.

The following year Ebaugh photographically demonstrated subarachnoid blood surrounding the medulla and pons of a patient with tuberculous meningitis who died following perforation of a posterior spinal vein during a cisternal puncture performed by an inexperienced intern.[5]

By 1929, Saunders and Riordan could report experience with more than two thousand cisternal punctures.[6] They described a patient with numbness on one side of his body for a week following puncture. After reviewing the seven reported deaths, two references to deaths, and the nine reported cases of probable medullary puncture with recovery in the literature at that time, they concluded that the procedure was safe in skilled hands but dangerous when attempted by the untrained.

Two deep puncture wounds of the medulla with bleeding into the fourth ventricle were demonstrated on pathologic examination by Vonderahe and Haberman[7] in a patient who became stuporous following an "unsuccessful" cisternal tap and died four hours later.

Goodhart and Savitsky[8] reported the case of a 24-year-old man with syphilis who felt "a shock like 10,000 volts" on his right side during cisternal tap, with subsequent extremity numbness, dizziness and headache. He was admitted the next day with pain and hyperthesia in the first division of the right fifth nerve and subarachnoid hemorrhage was demonstrated by lumbar puncture. The patient recovered promptly. The authors conjectured direct damage to the trigeminal descending tract in addition to the hemorrhage.

Dandy[9] described a 47-year-old man with general paresis who had headache with restlessness soon after a bloody cisternal tap and an hour later slipped into coma with Cheyne-Stokes respiration. At posterior fossa exploration six and a half hours after the tap, the cisterna magna was full of blood, which obstructed fourth ventricle outflow. An actively bleeding branch of the left posterior inferior cerebellar artery traversing low cerebellar tonsils was coagulated and the patient recovered completely. Dandy briefly mentioned a second case in which direct medullary puncture caused death within several minutes in a patient whose brain stem was displaced by tumor.

By 1949 Kehrer[10] was able to find 28 reports of death following cisternal puncture—most of them in the European literature. Two of the deaths resulted from definite medullary puncture and 21 involved subarachnoid hemorrhage. Kehrer added a further three cases of fatal hemorrhage and reported his own experience of four deaths in 8,835 punctures.

In Stender's case[11] the appearance of blood tinged cisternal fluid was followed by delayed progressive obtundation. At posterior fossa exploration, cisternal subarachnoid blood occluding the fourth ventricular foramina was removed and the patient had excellent recovery.

The patient reported by Schlorhaufer[12] experienced severe neck pain and sudden inability to speak during cisternal puncture but recovered over several days.

A 42-year-old man reported in the Swedish literature recovered from probable direct right medullary injury as well as subarachnoid hemorrhage requiring posterior fossa decompression in association with a cisternal puncture performed by an inexperienced physician.[13]

In 1964 Burzaco and Schisano[14] reported eight cases of severe post-puncture subarachnoid hemorrhage and noted three previous reports of surgical treatment in the literature.[9,11,15] Posterior-fossa decompressions were undertaken in all eight patients, with three surviving. In four of the cases bleeding came from ruptured branches of the posterior inferior cerebellar artery, and in the other four the site could not be demonstrated. The authors emphasized that some bleeding was evident in perhaps 5 percent of cisternal punctures and that progressive obtundation was the best guide to the presence of life-threatening hemorrhage. In one of their cases and several reported in the literature, the patients presented with late decompensation evidenced by pupillary changes, cranial nerve palsies, and obtundation three to eight days after puncture.

Zealear and Winn[16] described a probable cisternal puncture complication in a young man with coccidioidal meningitis who developed "deviation of the left eye laterally, increased deep tendon reflexes, nuchal rigidity and headache . . . at the time of . . . bloody cisternal and lumbar tap." He died four months later following an intraventricular amphotericin injection which produced lethargy, fever, nuchal rigidity and right facial paralysis. Besides evidence of active meningitis, diffuse subarachnoid hemorrhage was present at autopsy.

Intrathecal Amphotericin

The success of intravenous amphotericin B in the treatment of coccidioidal meningitis was demonstrated in several cases shortly after introduction of the drug.[17-19] To increase cerebrospinal fluid amphotericin levels without additional renal damage, Winn and others soon began combined intravenous and intrathecal treatment.[20] Winn came to favor the cisternal intrathecal route because of its more proximate location, and, although the injections were often attended by headache and vomiting in association with chemical meningitis, he felt the cisternal site preferable to lumbar injection with its arachnoiditis and frequent radiculopathy. The combined intravenous and cisternal approach has been widely accepted in treating coccidioidal meningitis and is occasionally used in other kinds of fungal meningitis.

There is no doubt of the efficacy of this treatment in suppressing infection, but there is little data on the precise benefits of the additional intrathecal administration. Frequent systemic infection precludes uses of intrathecal therapy alone, but several exacerbations of fungus meningitis have apparently responded to amphotericin given solely intrathecally.[20,21]

Current intrathecal amphotericin schedules vary considerably but Atkinson and Bindschadler's study of amphotericin cerebrospinal fluid levels in a single case suggests that the usual spacing of administration two or three times a week is suboptimal and that daily administration is required to maintain cerebrospinal fluid drug levels.[22]

Use of an Ommaya subcutaneous reservoir and intraventracular catheter is a technically appealing method of frequent intrathecal drug administration, but the complications of hemiparesis (as in Case 2), seizures, shunt blockage and secondary infection produce significant morbidity.[23]

All in all, the difficulties of intrathecal amphotericin administration by any route are sufficient to stimulate further inquiry into whether such therapy is virtually always required in coccidioidal meningitis or, in at least some cases, the disease could be adequately treated entirely intravenously pending discovery of a less toxic substitute for amphotericin.

Despite the risks of cisternal puncture, there will still be occasional need for a cisternal tap. When there is such need, only persons well trained in the technique should perform such procedures—preferably under fluoroscopic guidance—and only with ready access to emergency neurosurgical care.

Present evidence suggests that major post-puncture subarachnoid hemorrhage with progressive obtundation should be considered as an indication for emergency decompression of the posterior fossa.

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Coccidioidomycosis in Northern California

An Outbreak among Archeology Students near Red Bluff

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An outbreak of coccidioidomycosis occurred among 39 archeology students in the summer of 1972. The students excavated Indian ruins near Red Bluff in Tehama County, California, 20 miles north of the previously recognized northernmost limit of endemicity. At least 17 persons contracted an illness clinically compatible with a diagnosis of coccidioidomycosis. Coccidioidomycosis was documented by skin test conversion as well as by specific serologic reactions. Coccidioides immitis was also isolated from two soil samples taken at the excavation site. In light of its ecological requirements, it is doubtful that C. immitis will be recovered much farther north than Red Bluff. The occupational hazard of coccidioidomycosis to archeologists and others employed in known endemic areas remains a substantial threat to health.

COCCIDIOIDES IMMITIS, the fungal agent causing coccidioidomycosis, has never been isolated from soil obtained outside the Western Hemisphere.[1] In the United States, the disease is generally thought to be limited to the Southwest; and in California it is regarded as a problem of the southern half of the state and more particularly the San Joaquin Valley. Recently, however, outbreaks of coccidioidomycosis have been reported in Northern California, first in Yolo County[2] and then in Butte County.[3] This report discusses an outbreak of coccidioidomycosis which occurred some 20 miles farther north in Tehama County and now represents the most northerly endemic area for coccidioidomycosis known in California and the United States (Figure 1).

The Outbreak

A professor at California State University at Sacramento, who was leading an archeologic excavation on open, uncultivated land near Red Bluff, reported a suspected outbreak of coccidioidomycosis. The symptoms among his students were reminiscent of his own illness with coccidioidomycosis years previously. The outbreak involved at least 17 members of his party of 39 who partici-

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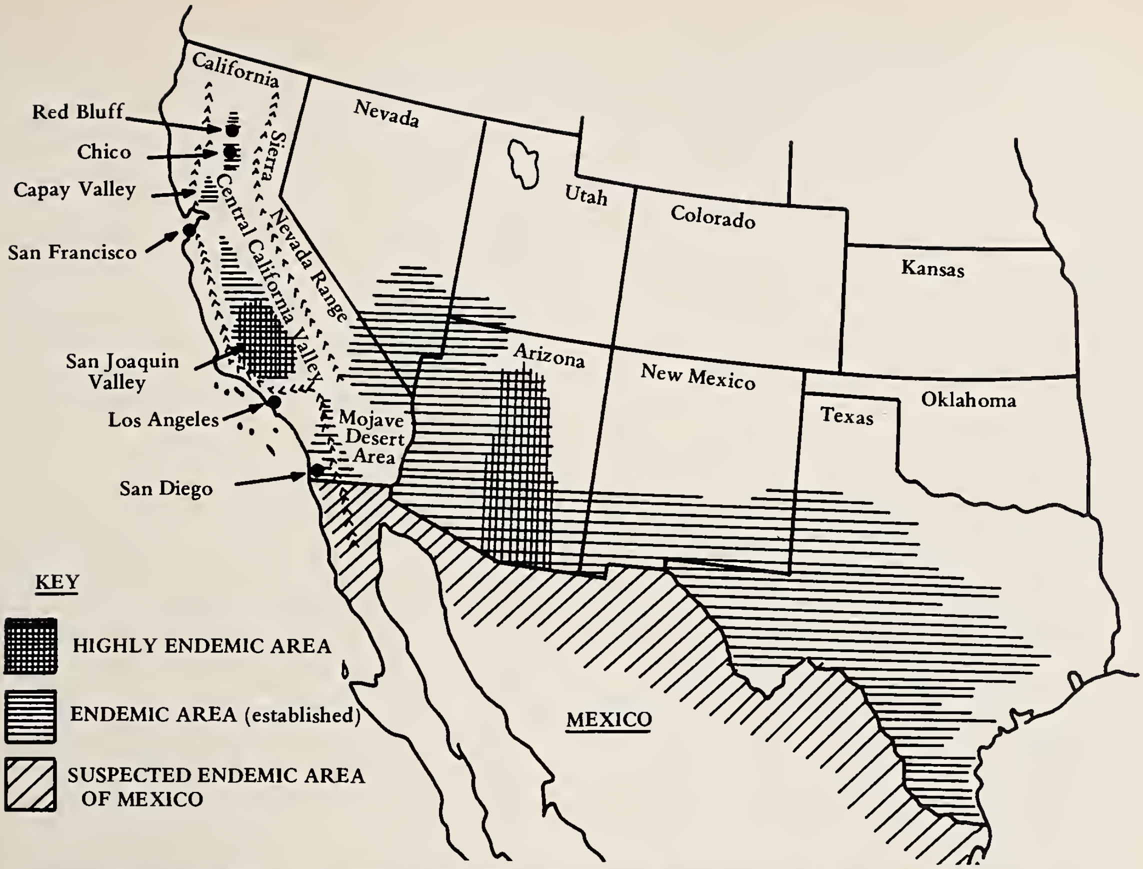
California
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New Mexico
Oklahoma
Texas
MEXICO
Red Bluff
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San Francisco
San Joaquin Valley
Los Angeles
San Diego
Sierra Nevada Range
Central California Valley
Mojave Desert Area
KEY
HIGHLY ENDEMIC AREA
ENDEMIC AREA (established)
SUSPECTED ENDEMIC AREA OF MEXICO

Adapted from Hinshaw, H.C.: Diseases of the Chest, Third Edition, Philadelphia, W.B. Saunders Company, 1969, with the permission of the publisher.

Figure 1.—Areas endemic for coccidioidomycosis in the United States and Northern Mexico.

pated in a six-week summer course. Most students were from out-of-state colleges and many had never before been in areas endemic for coccidioidomycosis. Excavation began 19 June 1972 for Indian ruins of the Yana civilization which resided in the Red Bluff area until about 1870. The only area the party excavated was at Dye Creek Ranch, 14 miles southeast of Red Bluff in Tehama County in the foothills of the Southern Cascade Mountain range at an elevation of 300 feet. Students excavated to depths averaging six feet. The soil was riddled with rodent burrows. Human skeletal remains were recovered, as were grinding tools and projectile points.

The summer, as usual, was hot with Red Bluff's all-time high of 119.3°F recorded 15 July 1972. The year preceding excavation had been drier than normal, only 10 inches of rain having fallen between 1 July 1971, and 30 June 1972, as compared with a normal annual total of 22 inches. The soil was dry and dusty; no masks were used. Students ate and slept in tents near the dig sites. The class was informed about the risk of contracting coccidioidomycosis before excavation began and members were skin-tested with coccidioidin by Dr. Susan Snively, director of the college Student Health Service. On 13 July, after four weeks of field work, illness was first reported.

Materials and Methods

On 17 July all participants in the archeology course were asked to complete a questionnaire and undergo laboratory studies.

Histories. In addition to demographic data, participants were asked if they had ever before been in states endemic for coccidioidomycosis. Both the participants and the Student Health Service were asked about reactions to the coccidioidin skin test given before fieldwork began. Those who reported any illness were asked to indicate their signs and symptoms on a checklist that was provided. In September 1972, follow-up questionnaires were sent to class participants for interim clinical histories.

TABLE 1.—*Symptoms of Clinical Coccidioidomycosis* Among 17 Archeology Course Participants (Red Bluff, California, 1972)*

Symptoms	*Number*	*Percent*
Cough	16	94
Shortness of Breath	14	83
Chest Pain	13	77
Myalgia	12	71
Headache	10	59
Sore Throat	9	53
Phlegm	8	47
Fever	6	35
Night Sweats	6	35
Rash	5	29
Meningismus	4	24
Chills	2	12
Abdominal Pain	2	12
Erythema Nodosum	1	6

*Presence of cough or chest pain was arbitrarily designated as the minimal criterion for a diagnosis of clinical coccidioidomycosis.

Laboratory studies included:

- *Radiographs* (posteroanterior films) of the chest.
- *Skin testing* with Coccidioidin 1:100 injected intradermally.
- *Serologic studies* for the presence of precipitins and complement-fixing (CF) antibodies to antigen from C. immitis.

Other laboratory studies included:

- *Animal trapping* at the excavation site for culture of C. immitis from lungs and lymph nodes.
- *Soil studies* for the fungal pathogen. Multiple specimens were obtained at the excavation site from topsoil (to a depth of 10 cm) and from the linings of rodent burrows. Soil specimens were collected on 17 July, 11 October, and 28 November 1972 until C. immitis was finally isolated. The specimens were collected in sterile containers and studied in two ways: (1) Soil suspensions were treated with penicillin and streptomycin, and were then inoculated intraperitoneally into mice, and (2) soil suspensions were treated with cycloheximide and streptomycin, then cultured using a double pour plate method with yeast extract agar containing cycloheximide and chloramphenicol.[4] Suspicious colonies were inoculated intraperitoneally in mice for confirmation.

Results

Questionnaire data:

Of the 39 participants, questionnaires were completed by 34. All but one were white; there were 17 men and 17 women. Of the 34 completing the questionnaire, 21 were from out of state and 13 denied ever having been in areas endemic for coccidioidomycosis.

Based on the diagnostic criterion of chest pain or cough, 17 of the 34 (or 50 percent) had begun to have illness compatible with coccidioidomycosis between 15 days after digging began and 18 days after digging ended. The attack rate for women (59 percent) was higher than that for men (41 percent). The peak date for onset of illness was July 10 — 21 days after fieldwork began. Table 1 details the symptoms reported by the 17 who were ill. None required admission to hospital.

Laboratory study results:

Radiographs. Abnormalities were detected in six of the 32 x-ray films taken. The six persons with x-ray abnormalities had been ill (Chart 1). The most common abnormality was hilar adenopathy with associated pneumonitis. One case had pleural effusion as well.

Skin testing. Thirty coccidioidin skin tests were evaluated at 24 and 48 hours after injection. Of 17 ill persons skin-tested with coccidioidin, nine (or 53 percent) had positive reactions of 5 mm of induration or more, as compared with two positive reactions (or 15 percent) among 13 persons who did not have symptoms. Eight of the nine positive reactions among ill persons represent conversions from negative reactions recorded at the start of the course. One ill person with a positive reaction had not had a coccidioidin test before the course began. Two persons who had had positive coccidioidin reactions before excavation began remained well throughout the study period.

Serologic studies. Thirty-three had serologic studies. Of 17 ill persons tested, seven (or 41 percent) had serologic evidence for coccidioidomycosis compared with no positives among 16 well persons tested (Chart 1). Six persons had positive precipitin test reaction. Of these, five were also positive by CF. One person had a positive CF test but a negative precipitin test. No CF titer was greater than 1:8.

Results of animal trapping and culture. Four gray field mice were trapped alive and then killed for study. C. immitis could not be isolated from them.

Soil studies. Of a total of 22 specimens of soil collected, only two were positive. Both were col-

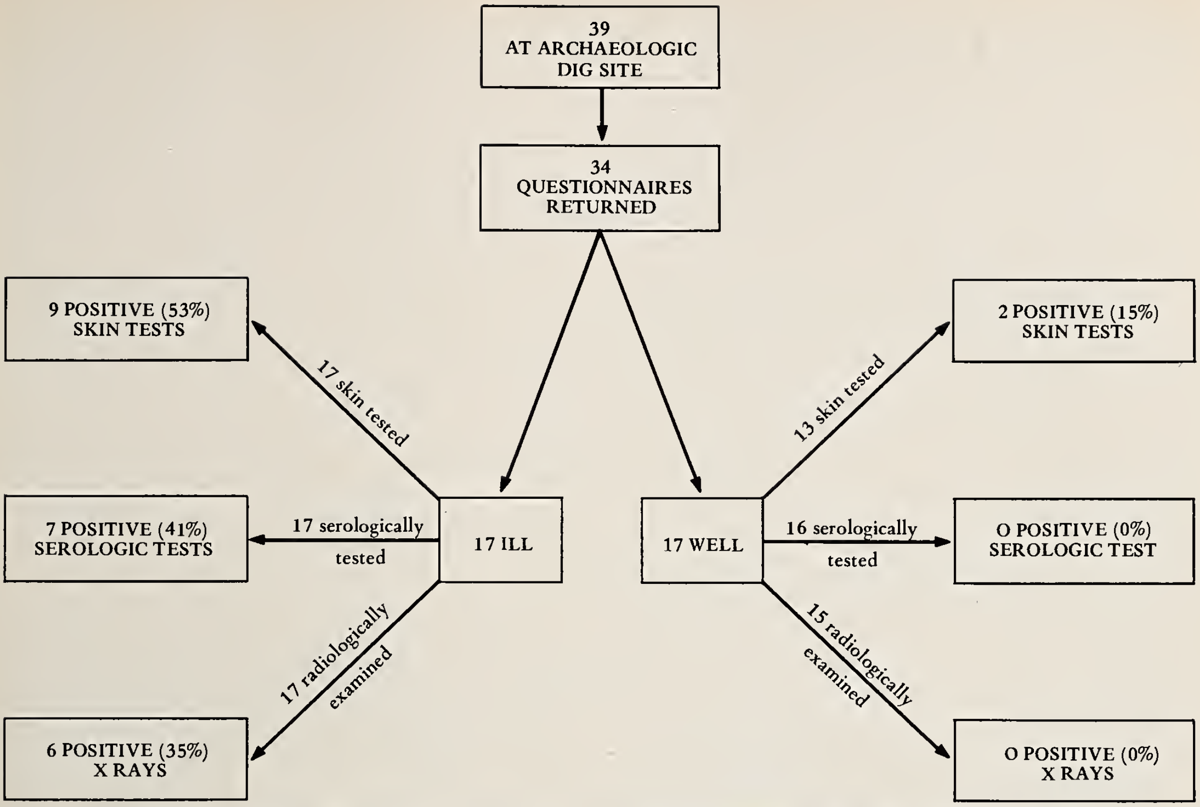
39
AT ARCHAEOLOGIC DIG SITE
34
QUESTIONNAIRES RETURNED
17 ILL
17 WELL
17 skin tested
9 POSITIVE (53%) SKIN TESTS
17 serologically tested
7 POSITIVE (41%) SEROLOGIC TESTS
17 radiologically examined
6 POSITIVE (35%) X RAYS
13 skin tested
2 POSITIVE (15%) SKIN TESTS
16 serologically tested
O POSITIVE (0%) SEROLOGIC TEST
15 radiologically examined
O POSITIVE (0%) X RAYS

Chart 1.—Summary flow sheet of findings for coccidioidomycosis, Red Bluff, California, 1972.

lected on 28 November 1972. One of the positives resulted from direct mouse inoculation, with isolation of C. immitis from cultures of typical lesions. A direct soil culture was also positive; suspicious colonies were confirmed by intraperitoneal inoculation of mice with demonstration of endosporulating spherules in lesions of thoracic and abdominal cavities.

Discussion

This outbreak identifies a new area of endemicity for coccidioidomycosis in Northern California, farther north than ever before recognized. It emphasizes again the risk of coccidioidomycosis to susceptible persons with extraordinarily heavy exposure to contaminated soil.

Of 34 respondents, half reported illness clinically compatible with coccidioidomycosis. The laboratory data leave no doubt that the outbreak was due to coccidioidomycosis. Not only were there documented conversions of coccidioidin reaction among eight ill persons, but positive serologic tests to C. immitis were found exclusively among those who were ill. Finally, C immitis was isolated from soil taken from the excavation site.

Only ten of the 17 persons with illnesses clinically compatible with coccidioidomycosis had laboratory confirmation (positive coccidioidin test or serologic test). The other seven may have had some other respiratory disease or may have been tested too soon in the course of illness for results to be positive. The peak of the outbreak occurred on 10 July 1972, just seven days before skin test agents were injected and sera collected. Smith et al[5] reported that coccidioidin skin tests may not turn positive until two to three weeks after clinical onset. Smith also reported that demonstrable humoral antibodies may never develop in mild cases[6] and that when they do, CF antibodies are especially late to appear.[7] Less than one-third of patients with coccidioidomycosis in whom CF antibodies ultimately develop give evidence of the fact within the first month of illness.[8] Maddy suggested that C. immitis is limited to the geographic area of the lower Sonoran Life Zone which is characterized by arid and semi-arid climate, hot summers, few winter freezes, sparse flora, low altitude, and alkaline soil.[9] Red Bluff is representative of this zone, and indeed Grinnell stated in 1935 that this zone extends only as far north as Red Bluff.[10] In view of its ecologic requirements, it is doubtful that C. immitis will be recovered much farther north than Red Bluff.

Influenza-like illness with concurrent rash provided the early clue that this archeology class was undergoing an outbreak of coccidioidomycosis. This combination of symptoms should bring coccidioidomycosis to mind in the differential diagnosis of disease in patients from areas known to be endemic and from areas nearby.[11]

The symptoms reported in this outbreak (Table 1) were comparable in type and frequency with those we reported in a larger outbreak.[3] Fortunately, morbidity was less in the present group and none of the patients needed treatment in a hospital. Indeed, CF titer did not exceed 1:8 in any case. Smith had previously noted that serious disease, such as dissemination, is associated with titers greater than 1:16.[8]

In an effort to acquaint archeology programs in California with the risk of acquiring coccidioidomycosis, letters were sent by the California State Department of Public Health in November of 1970 to every college in California with an archeology or anthropology program, and each was provided basic recommendations. However, as outbreaks continued to occur among archeology students, some of whom were quite ill and bringing litigation against their respective institutions, a more complete list of recommendations was distributed in September 1972 to the presidents of all California colleges for distribution to all departments (archeology, geology, anthropology, engineering, and others) in their institutions offering fieldwork. These recommendations are detailed elsewhere[12] and, if implemented, should reduce the incidence of coccidioidomycosis in future groups. The recommendations are summarized below:

1. No educational institution should require fieldwork in areas endemic for coccidioidomycosis.
2. Information should be provided on coccidioidomycosis (specific references were provided).
3. Coccidioidin skin tests should be performed to determine those at risk of illness.
4. Nonreactors should be advised not to participate in fieldwork in areas endemic for coccidioidomycosis.
5. Dust control should be exercised wherever feasible, including use of masks, working and sleeping upwind of excavation sites, and other measures deemed reasonable after assessing the specifics of each situation.

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Specialty Conference

Refer to: Ross J Jr, O'Rourke RA, Peterson KL, et al: Non-invasive methods for the assessment of cardiac function (Specialty Conferences). Calif Med 119:21-37, Sep 1973

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Non-Invasive Methods for the Assessment of Cardiac Function

DR. JOHN ROSS, JR.:* Since Cournand and Richard's implementation of precise methods for hemodynamic study of the right side of the heart, direct cardiac catheterization has remained the standard tool for the assessment of circulatory dynamics. The subsequent development of methods for entering the left side of the heart and for selective angiocardiography, together with further improvements in instrumentation, have added to the usefulness and further improved the precision of such techniques. Nevertheless, these invasive procedures carry the risk of catheter-induced vascular and cardiac complications, and the search for suitable non-invasive methods for examination of the heart and circulation has been a continuing one. There remains a clearcut need for techniques that will permit study of cardiac patients in serial fashion, and during various forms of stress, reliably and without hazard.

The present conference will focus on several types of non-invasive studies that have seen substantial advances in the past few years. In examining the usefulness of each of these approaches it is desirable, of course, to test their validity against the standardized invasive methods of cardiac catheterization and angiography, and each of the investigators participating in this conference has directed some attention toward this goal. The non-invasive techniques that we shall examine today include external recording of the pulse waves and heart sounds (the so-called systolic time intervals); plain radiographic and video techniques for examining heart size and motion; the use of ultrasound for obtaining dynamic anatomic information about the heart and great vessels; and the use of radioisotopes.

The recording of an indirect carotid pulse wave tracing, together with the electrocardiogram and a recording of the heart sounds, constitutes one of the earliest methods used for estimating the

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functional state of the left ventricle. Several recent studies have shown good statistical correlations between the angiographic methods for evaluating left ventricular function and the systolic time intervals. Dr. Robert O'Rourke will open the discussion by reviewing the current status of these methods and some of the factors that influence their reliability.

Dr. Robert O'Rourke:* The indirect measurement of the pre-ejection period (PEP) and the left ventricular ejection time (LVET), often termed the systolic time intervals (STI), has found increasing use in patients with a variety of cardiac disorders. Studies in several laboratories suggest that measurement of the STI may provide a non-invasive yet sensitive means for detecting depression of left ventricular function, particularly when applied serially in the individual patient.[1-5] In addition, the STI clearly can distinguish groups of patients with left ventricular failure from normal subjects; however, they appear less reliable for separating patients with compensated heart disease from normal subjects, either under resting conditions or during exercise.[6] Moreover, the STI can be influenced by a number of hemodynamic variables, several of which may be operative simultaneously in a given subject. Therefore, considerable controversy remains as to the accuracy with which the STI reflect left ventricular function in the individual cardiac patient.[6,7]

The measurement of left ventricular STI requires the simultaneous recording of a high frequency phonocardiogram, the indirect carotid arterial pulse waveform, and the electrocardiogram on a multichannel recorder at a paper speed of at least 100 mm per second. The recordings are made with the subject supine and in the basal, post-absorptive state.[1,3] Calculations of the mean systolic time intervals are based upon the measurement of at least ten cardiac cycles, beginning and ending with the same phase of respiration.

Electromechanical systole (Q-S$_2$ interval) encompasses the period from the onset of the QRS complex to the first high frequency deflection of the aortic component of the second heart sound (Figure 1). The left ventricular ejection time (LVET) begins with the upstroke of the carotid arterial pulse and ends with the dicrotic notch (Figure 1). This interval correlates closely with the same interval measured from the intra-aortic pressure pulse tracing. The pre-ejection period (PEP) is the difference between the duration of left ventricular electromechanical systole and the LVET, that is, PEP = (Q-S$_2$)-LVET. The PEP can be further divided into the Q to S$_1$ interval and the period of isovolumetric contraction (ICT).

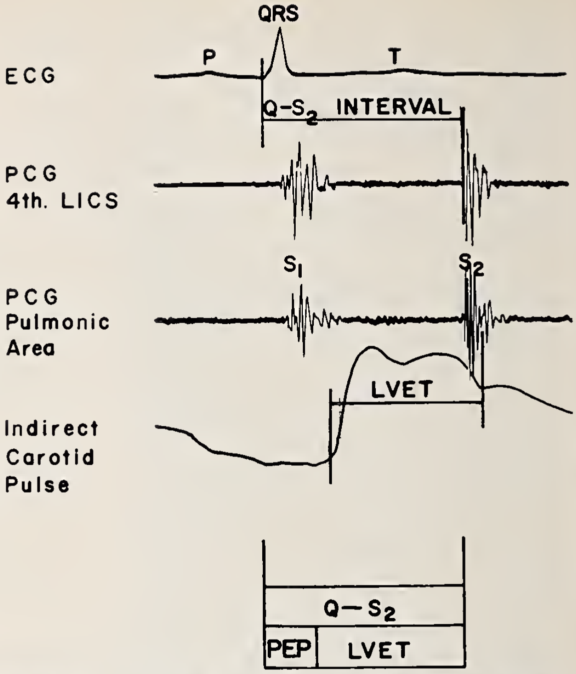

Figure 1.—Systolic time intervals in a normal subject. ECG is the electrocardiogram; PCG, the phonocardiogram; LVET is the left ventricular ejection time; PEP is the pre-ejection period; and Q-S$_2$ is electromechanical systole. LICS is left intercostal space. (From Johnson AD, O'Rourke RA, Karliner JS, and Burian C: Effect of myocardial revascularization on systolic time intervals in patients with left ventricular dysfunction. Circulation 45 (Suppl 1):91, 1972. Reproduced by permission of the American Heart Association, Inc.)

Factors which influence the LVET include the heart rate, stroke volume, left ventricular afterload, the myocardial inotropic state, and the sex of the patient (Figure 2).[1,2] Unfortunately, in the individual patient there may be changes in several of these variables simultaneously, each change having a different effect on the left ventricular ejection time. For example, the administration of a positive inotropic agent such as digitalis to a patient with left ventricular failure and a diminished stroke volume would have two opposite effects on the LVET. The increase in stroke volume resulting from the increase in myocardial contractility would tend to increase the LVET while the increase in the velocity of ventricular ejection would tend to shorten it.

Factors which influence the PEP include heart

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FACTORS INFLUENCING SYSTOLIC TIME INTERVALS

↑ PEP I	• LV FAILURE • ELEVATION IN DIASTOLIC ARTERIAL PRESSURE • DIMINISHED LV FILLING PRESSURE • NEGATIVE INOTROPY • LV CONDUCTION ABNORMALITY	• INCREASE IN STROKE VOLUME • ELEVATION IN LV SYSTOLIC PRESSURE • AORTIC VALVE DISEASE	↑ LVET I
↓ PEP I	• DECREASE IN DIASTOLIC ARTERIAL PRESSURE • INCREASED LV FILLING PRESSURE • POSITIVE INOTROPY	• LV FAILURE • DECREASE IN STROKE VOLUME • POSITIVE INOTROPY	↓ LVET I

Figure 2.—Schematic representation of the effects of various hemodynamic alterations on the pre-ejection period index (PEP I) and the left ventricular ejection time index (LVET I).

rate, aortic diastolic pressure, the duration of the QRS complex, left ventricular filling pressure, and the inotropic state of the myocardium (Figure 2).[1,2] Accordingly, in patients with cardiogenic shock, a high left ventricular end-diastolic pressure and a low aortic diastolic pressure may result in a short PEP despite depressed left ventricular function. On the other hand, a normally or mildly elevated left ventricular end-diastolic pressure and a normal aortic diastolic pressure usually is accompanied by appreciable prolongation of the PEP when myocardial contractility is depressed, because of the reduced rate of isovolumic pressure development (dP/dt).

Systolic time intervals can be corrected for both heart rate and the patient's sex by using regression equations derived from data obtained in a large number of resting subjects without evidence of heart disease. Currently, there are no equivalent data on the relationship of STI to heart rate in normal subjects during supine and upright exercise. In the resting subject, the ratio of the PEP to the LVET (PEP:LVET) varies within narrow limits and need not be corrected for heart rate or sex. Deviations of PEP, LVET and QS_2 from normal may be represented by the difference between the observed measurements, uncorrected for heart rate and sex, and those predicated for the patient's heart rate and sex from the appropriate regression equation.[1,2] Another method of evaluating these measurements is to correct the observed values for heart rate and sex (systolic time interval indices) and compare the results to the normal range of corrected values.[1,2] The STI indices are calculated as the sum of the measured intervals and the product of the observed heart rate and the appropriate normal regression slope. For example, the LVET index in male subjects = 1.7 heart rate (HR) + the measured LVET (Table 1).

During left ventricular failure the PEP lengthens, the LVET diminishes, and the duration of electromechanical systole remains unchanged. These altered relationships may be expressed as an increase in the PEP:LVET ratio during left ventricular failure. The normal ratio in the basal state is 0.345 ±0.036 (1SD).[3] Several studies have shown a significant inverse correlation between the PEP:LVET ratio and the ejection fraction (stroke volume/end-diastolic volume) obtained by left ventricular cineangiography in patients with a variety of cardiac diseases.[3,5] In the presence of left ventricular failure, the increased pre-ejection period reflects the diminished rate of myocardial tension development, and the diminished left ventricular ejection time reflects the decreased stroke volume and reduced rate of myocardial fiber shortening.

Recently, we compared STI with measurements of the left ventricular ejection fraction (stroke

TABLE 1.—*Systolic Time Indices in Normal Subjects**

Measurement	*Equation*	*Normal Range*
$Q\text{-}S_2$ index (male)	$Q\text{-}S_2$ interval + 2.1 HR	530 - 560 msec
$Q\text{-}S_2$ index (female)	$Q\text{-}S_2$ interval + 2.0 HR	same
LVET index (male)	LVET interval + 1.7 HR	408 - 428 msec
LVET index (female)	LVET interval + 1.6 HR	same
PEP index (male)	PEP interval + 0.4 HR	118 - 144 msec
PEP index (female)	PEP interval + 0.4 HR	same

*HR is the heart rate and msec is milleseconds.

volume/end-diastolic volume) and the mean velocity of circumferential fiber shortening (mean Vcf) as measured from biplane left ventricular cineangiograms in patients with coronary artery disease or primary myocardial disease.[8,9] The direct and indirect studies were made on the same day in each patient. The results showed a good inverse correlation between the PEP:LVET ratio and the left ventricular ejection fraction (LVEF) ($r = -0.77$, $p < .001$) and the mean rate of circumferential fiber shortening (mean Vcf) ($r = -0.60$, $p < .001$). The correlation between PEP:LVET and either LVEF or mean Vcf was similar in patients with or without abnormal left ventricular wall motion. In this study, as in others, the measurement of STI clearly separated a group of normal patients from a group of patients with moderate or severe depression of left ventricular function. However, discordant results between STI and cineangiographic measurements of left ventricular function often occurred in individual patients within both groups. STI measurements suggested depressed left ventricular function in several patients with normal LVEF and mean Vcf, and were normal in other patients with cineangiographic evidence of reduced left ventricular function. This finding is not surprising considering the number of variables that can influence the measured STI, and the large standard deviation for the normal ratio of PEP:LVET.

We have found the serial measurement of STI to be useful in following individual patients with coronary artery disease and for evaluating the effect of interventions (vein bypass graft operation, propranolol therapy) on left ventricular function.[10,11] However, in several instances we have observed changes in STI which were not substantiated by a repeat left ventricular cineangiographic study, and occasionally *no* alterations occurred in STI despite pronounced reduction in left ventricular function on repeat cardiac catheterization after operation.

We may conclude that measurement of STI provides a useful means for the non-invasive evaluation of left ventricular function, particularly for separating groups of normal patients from patients with moderate to severe depression of left ventricular function. However, the available data suggest that the STI cannot always separate the individual patient with cardiac disease and mild to moderate left ventricular dysfunction from the subject with normal cardiac function. The major problem in interpreting STI, even in the same patient during periods of follow-up, is the difficulty in accounting for all of the hemodynamic variables that may be operative at the time of a given measurement. Nevertheless, serial recordings of the STI provide a non-invasive means for patient follow-up that often can alert the physician to the presence of depressed left ventricular function, and also add confidence to a clinical diagnosis of normal cardiac function.

Dr. Ross: Perhaps the first non-invasive means for examination of the heart, if we used the term non-invasive to indicate lack of intravascular catheter insertions, was the diagnostic chest x-ray film, and subsequently electrokymography also found considerable application. At the conference on myocardial infarction two years ago[12] we reviewed the use of standardized plane roentgenographic techniques for assessing left ventricular size, as well as radarkymography, a technique which employs a radar tracking circuit during image intensification fluoroscopy for obtaining an analog signal of cardiac wall motion. Drs. Kirk Peterson and Philip Ludbrook now have had considerable experience with an improved device for assessing wall motion abnormalities by use of a video-radiographic method and will describe the current status of this approach.

DR. KIRK PETERSON* AND DR. PHILIP LUDBROOK:† The analysis of left ventricular wall motion is of significant importance in the evaluation of the hemodynamics and mechanics of contraction in various cardiac disease states. Left ventricular cineangiography has provided the most direct and accurate means of recording wall motion in man,[13] but it is limited by its dependence on cardiac catheterization, lack of applicability to acutely ill patients, and unsuitability for serial observations. Non-invasive radiographic methods, including roentgenkymography and electrokymography,[14-16] have been used in the past but their successful application was hampered by lack of resolution, alinearity, poor frequency response or impracticability of operation. Apexcardiography and kinetocardiography[17,18] likewise are limited because the area of left ventricle examined is small and because of signal degradation imposed by the intervention of the chest wall between the heart and the recording transducer.

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The recent development of video-tracking devices now provides a reliable and relatively sensitive method for assessing left ventricular wall motion without the need for intracardiac instruments or catheters.[19,20] Such devices have proved useful for detecting the presence or absence of areas of segmental wall motion disorder, for assessment of serial changes in hypokinesis or dyskinesis during the course of an acute myocardial infarction, and for elucidation of the effects of pharmacologic agents on regional myocardial contraction.[21-23] They have future potential for non-invasive detection of abnormal diastolic filling patterns, quantitation of left ventricular compliance or distensibility and assessment of extent and velocity of myocardial shortening. In initial clinical studies, the Radarkymograph (RKY)* was used.[19] More recently, an improved Video Dimension Analyzer (VIDIAN)† with superior frequency response and ease of operation has been employed for microvascular studies in animals[20] and is now used in our laboratory for the study of cardiac pathophysiology in man.[21]

The black-white interface of the border of the heart and lung recorded during fluoroscopy is transmitted to the television circuit along each raster line as a change in voltage. When differentiated, this signal can be captured by the tracking circuits of the RKY, or the VIDIAN, which then generates an analog signal proportional to the motion of the black-white interface (Figure 3). The RKY is a device which records relative change in position of the border of the heart but does not provide absolute measurement of changes in position unless it is calibrated with an object of known size. The VIDIAN is a dual-window device capable of rapidly tracking with independent thresholds for either one or both sides of a moving object. The time lapse between the triggering of the two windows is proportional to the dimensions of the object delineated, thereby providing a continuous measurement of the extent of ventricular wall excursion. By recording the analog signal of wall motion on an oscillograph, the velocity of the ventricular wall excursion also can be determined.

As shown in Figure 4, the normal motion of the lateral external wall of the left ventricle recorded by the VIDIAN is characterized by: (1) an upright "a" wave (occurring 80-120 msec after the onset of the p wave on the apexcardiogram and coincident with the fourth heart sound as recorded by phonocardiography); (2) a second small positive deflection commencing simultaneously with the phase 1 component of the first heart sound (the rapid ascent ["C" point] of the apexcardiogram, and the initial rise of isovolumic pressure in the left ventricle following atrial contraction); (3) a downward deflection during ejection which begins with the initial upstroke of the high fidelity ascending aortic pressure pulse (coincident with the "E" point of the apexcardiogram) and ends after the notch on the ascending aortic pressure pulse; and (4) a diastolic phase marked by an initial steep ascent (corresponding with rapid filling wave of the apexcardiogram and ending with the third heart sound, as recorded on the phonocardiogram) and followed by a considerably more shallow ascent often punctuated by low frequency oscillations (Figure 4).

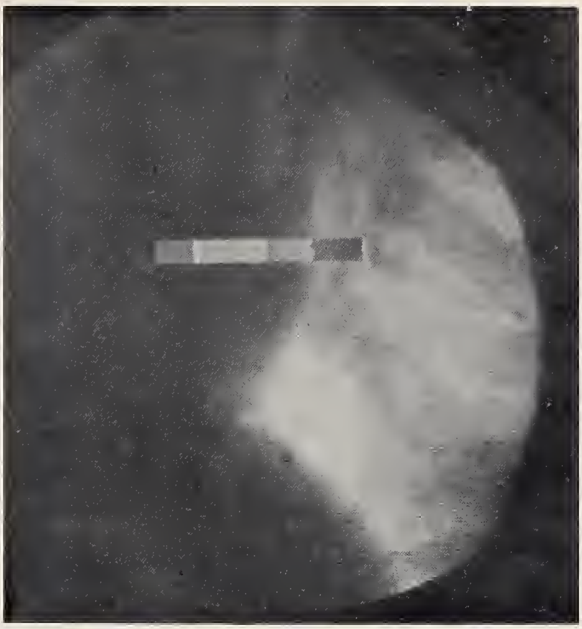

Figure 3.—Videodimension analyzer (VIDIAN) tracking fluoroscopic image of left heart border on television monitor. In practice the image is rotated so that long axis of left ventricle is perpendicular to raster lines of television. Left-hand window is stationary; right window is tracking the dynamic changes in position of left heart border.

Previous clinical studies of patients with acute myocardial infarction have determined that hypokinetic and dyskinetic areas of ventricular wall, some of which were not recognizable by the human eye, can be reliably detected with video-tracking (Figure 5). Moreover, wall motion abnormalities could not be visualized by fluoroscopy in 16 of 32 patients with chronic coronary artery disease in

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*Manufactured by Biotronix, Silver Spring, Maryland.

†Manufactured by UCSD, Department of Bioengineering.

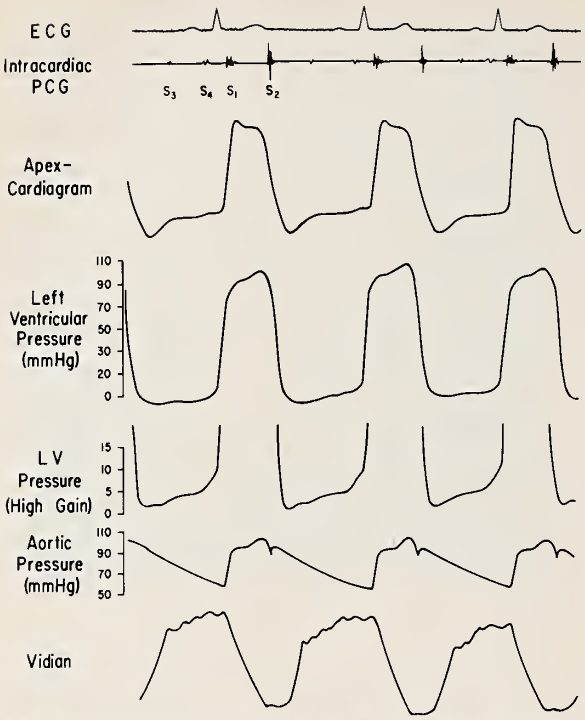

Figure 4.—Relative time sequence of electrocardiogram, intracardiac phonocardiogram, apexcardiogram, left ventricular pressure, ascending aortic pressure, and VIDIAN track of left ventricular wall (left anterior oblique projection). Note the rapid, slow, and atrial filling phases during diastole on the VIDIAN trace.

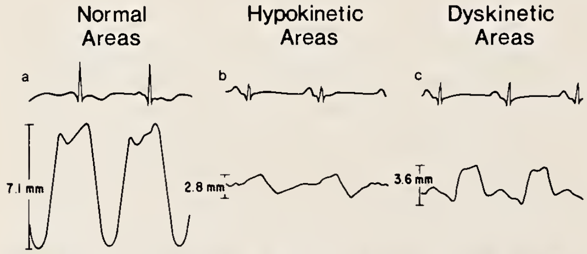

Figure 5.—Comparison of RKY tracking (lower panel) of normal (left), hypokinetic (center), and dyskinetic (right) areas of left ventricular wall. Electrocardiogram on top panel provided for timing of cardiac events.

whom such disorders could be detected by video-tracking. Areas of asynergy shown on left ventriculography in 18 patients were likewise reliably detected by radarkymography in 16 of the subjects.[22]

Recent observations on the response of the left ventricle to hand grip exercise (where heart rate and systemic arterial pressure increase) suggest that this intervention is useful for eliciting latent wall motion abnormalities or exaggerating preexistent ones in patients with coronary heart disease.[23] Areas along the anterior and apical-lateral surface of the left ventricle are more readily detected than those along the inferior wall where the diaphragm inhibits clear delineation of the ventricular margins.

Video-tracking also has been used as a non-invasive means for the evaluation of the response of left ventricular wall motion to pharmacologic interventions, and we have recently studied the effects of beta-blockade on the characteristics of both normal and abnormal wall motion following intravenous administration of propranolol. It has been suggested that wall motion abnormalities may be worsened by propranolol. However, in areas which initially displayed dyskinetic or asynchronous outward movement, the amplitude and velocity of excursion were decreased by propranolol, resulting in a net diminution of the degree of outward bulging—that is, a net improvement in abnormal wall motion.[24] In areas of normal or hypokinetic wall motion, we found significant reductions in both the amplitude of the excursion and in the velocity of movement using the VIDIAN system.

A further use of video-tracking is in the study of diastolic filling patterns of the left ventricle. Comparisons of the shape and timing of the VIDIAN signal from the high lateral left ventricular wall margin in the left anterior oblique projection with ventricular volume measurements throughout the cardiac cycle have shown a striking similarity (Figure 6). Thus, a non-invasive determination of relative changes in ventricular dimensions by video tracking may prove to be a reliable method for recognizing those conditions with impeded ventricular filling—for example, constrictive pericarditis, mitral stenosis, or restrictive cardiomyopathy. When such diastolic filling curves are recorded with a simultaneously obtained diastolic left ventricular pressure, a beat-by-beat analysis of ventricular compliance and stiffness also is feasible (Figure 7). Assuming an exponential relationship, the slope of the plot of the natural logarithm of pressure versus the relative change in the left ventricular minor axis dimension, as measured by the VIDIAN, during the slow phase of ventricular filling, provides a coefficient of elasticity for the ventricle.

Video-tracking now provides an objective and quantitative non-invasive method for assessing the mechanical properties of the left ventricular wall during both systole and diastole. Abnormalities of

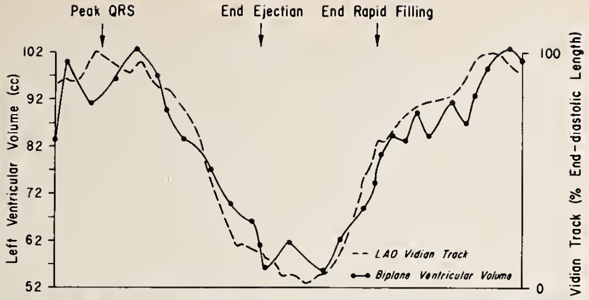

Figure 6.—Comparison of VIDIAN track of left heart border (dashed line) with measurement of left ventricular volume (solid line) throughout cardiac cycle.

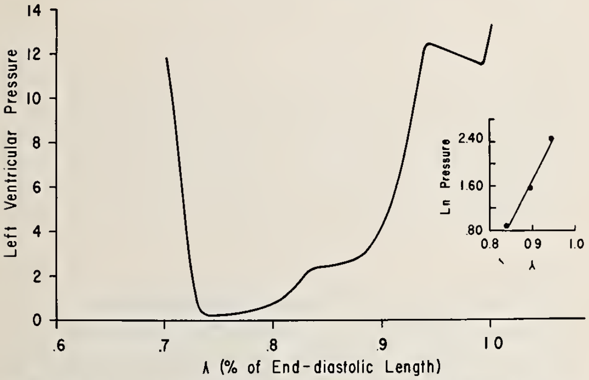

Figure 7.—High-fidelity left ventricular pressure (abscissa) plotted against percent of end-diastolic length (λ) (ordinate) throughout isovolumetric relaxation and diastole. Insert in right-hand corner depicts plot of natural logarithm of pressure versus λ during slow-filling phase of diastole. Rapid filling due to atrial contraction occurs between λ of 0.9 and 1.0.

the systolic contraction pattern appear to be more readily detected by video-tracking than by simple fluoroscopy alone and correlate reliably with findings on left ventriculography. Diastolic filling patterns, formerly assessed only by apexcardiography or tedious calculation of diastolic volumes from a cineventriculogram, can now be assessed by tracking the lateral left ventricular margin. The technique thus affords a new means of assessing ventricular function and filling, properties of particular importance to the understanding of cardiac performance in various forms of heart disease.

Dr. Ross: Another radiographic technique which employs only a plain, standardized chest roentgenogram recently was developed in our laboratory, and has now found considerable application in the serial follow-up of left ventricular size in cardiac patients and in the assessment of responses to pharmacologic interventions. Dr. Crawford has made several practical applications of this approach.

Dr. Michael Crawford:* Left ventricular volume is an important factor in regulating cardiac performance, and the size of the left ventricle also has significant implications relative to the diagnosis and management of a variety of cardiovascular disorders. It would be useful, therefore, to have available a non-invasive method by which left ventricular size could be determined accurately and reproducibly. Plain radiographic techniques have the advantage of technical simplicity and widespread availability of equipment. The cardiothoracic ratio is commonly employed, although it has limitations because of its dependence upon thoracic configuration and because it does not specifically measure the left side of the heart.[25] Other plain radiographic techniques for calculating cardiac size and volume are more accurate,[26] but unlike the cardiothoracic ratio they require upright lateral films, prohibiting their application in acutely ill patients, and limiting their usefulness for assessing the heart under basal conditions. The need for an accurate technique for examining the left ventricle in such patients has led to the development of a standard technique for measuring the external left heart size.[27]

A frontal chest roentgenogram is taken with the patient in a horizontal position (or at a 45° angle, if necessary), small lead markers being taped to the chest at the sternal notch and xyphoid process. A small hand-held respirometer is used to insure a standard inspiratory volume of one liter above functional residual capacity, and the chest roentgenogram is triggered from the electrocardiogram to be exposed at end-diastole.[27] Subsequently, a vertical line is drawn on the film connecting the two lead markers, and a second, parallel vertical line is drawn tangential to the widest point of the left ventricular silhouette (Figure 8). The horizontal distance between these two lines, corrected for x-ray magnification and normalized per square meter of body surface area (m^2 BSA) represents the left heart dimension (LHD).

As with any plain radiographic technique, the LHD cannot be determined accurately in patients with a left pleural effusion, pericardial effusion, or pulmonary infiltrates that obscure the left heart border. This technique also may be unreliable in patients too dyspneic to hold their breath momentarily. Further, one must be careful that the patient does not perform a Valsalva maneuver, which is known to decrease heart size. Occasionally, pronounced elevation of the diaphragm or extreme enlargement of the right side of the heart may increase the LHD. With these precautions, the LHD has been found to be a reproducible and reliable measure of left ventricular size.[27]

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*Dr. Michael Crawford is a Post Graduate Cardiology Trainee and Instructor of Medicine.

One major use of the LHD measured in the basal, supine state is to determine whether or not left ventricular size is normal or abnormal in the individual patient. The LHD was found to correlate closely with left ventricular diameter (LVD) measured by cineangiographic techniques,[27] LVD being related to LHD by the regression equation $\mathrm{LVD} = 0.46\ \mathrm{LHD} + 23.5$ mm ($r = 0.78$, $p < 0.001$). The average value for LHD in normal persons was found to be 44±4 mm (1SD) per m^2 BSA and the upper limit of normal is considered to be 52 mm per m^2 BSA (+2 SD) (Figure 8). The LHD is routinely determined on admission to the Myocardial Infarction Research Unit at our institution and has been shown to be a valuable predictor of early and late survival after acute myocardial infarction. For example, early death occurred six times more frequently in those with an initially abnormal LHD ($p < .001$).[28]

Since the LHD is relatively unaffected by slight degrees of rotation of the patient, it has been a reliable technique for serial studies. During late follow-up after recovery from acute myocardial infarction, averaging ten months, patients with a persistently abnormal LHD had five times the death rate of those with a normal LHD. With one exception, all patients in New York Heart Association (NYHA) Class I-II had a normal LHD and the majority in NYHA Class III had an abnormal LHD.[28] Thus, the LHD has been a practicable method for serial studies and has proven useful for estimating survival and morbidity, as well as for effectively following the clinical course after an acute myocardial infarction.

In the cardiac catheterization laboratory a close correlation between the LHD and cineangiographic measurement of actual left ventricular diameter was shown to exist when changes in left ventricular volume were induced by acutely altering afterload, and other manipulations.[27] Therefore, another important application of the LHD has been to evaluate non-invasively the effects of various physiologic and pharmacologic interventions on the size of the left ventricle. For example, the normal response to submaximal isometric handgrip exercise is a small decrease in LHD.[29] In patients with a previous myocardial infarction NYHA Class I or II without major wall motion abnormalities, the LHD also decreased with handgrip, but in symptomatic patients (NYHA Class III) with major wall motion abnormalities the LHD usually increased. Thus, this measure provides a useful means of detecting an abnormal myocardial response to this physiologic stress.

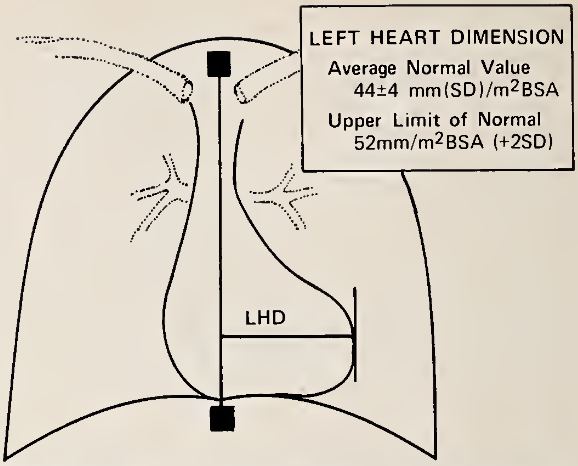

Figure 8.—Method for determining the external left heart dimension (LHD) from plain ECG triggered roentgenogram. The black squares indicate lead markers in the mid line between which a vertical line is drawn, the LHD representing the distance from the mid line to the widest point on the left heart border.

The LHD also has been used to assess the effects of pharmacologic interventions on ventricular size and performance. The administration of propranolol intravenously has been shown to cause an increase LHD in patients with coronary heart disease by a mean of 3±7 (SD) mm ($p < .001$).[30] Preliminary results from our laboratory show that there is a small but significant increase in the LHD in patients with coronary heart disease who are taking oral propranolol as well. In some patients, this increase was reversed by adding a digitalis preparation. Figure 9 shows the values of LHD in a representative patient after two weeks of therapy with these drugs. The initial LHD was abnormal, and it was significantly increased further by propranolol therapy, an effect due at least in part to the observed slowing of heart rate; however, the addition of digoxin tended to reverse this increase. Thus, this approach can permit investigation of the effects of various pharmacologic agents on left ventricular size, as well as allow the selection of an optimal therapeutic program.

In conclusion, the left heart dimension has proved to be an accurate yet practical, non-in-

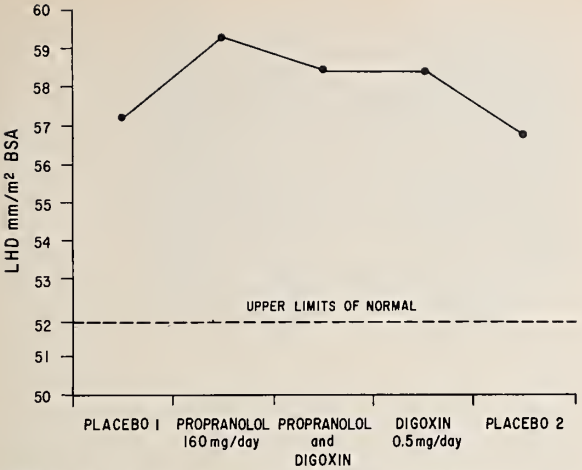

Figure 9.—Response of the left heart dimension (LHD) to two-week periods of oral drug therapy (each vertical line represents two weeks). The upper limits of normal (52 mm per M^2 BSA) for the left heart dimension is shown in this patient, who has marked left ventricular enlargement. The increase in left heart size induced by propranolol is partially reversed by digoxin therapy.

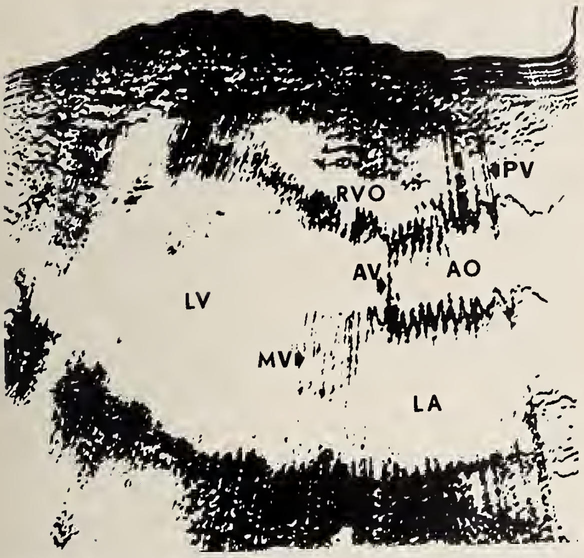

Figure 10.—Non-stop action B-scan made along the left fourth intercostal space in a patient with multichamber enlargement. The right-hand side of the picture shows the aortic root while the left side ends near the cardiac apex. LV = left ventricle, RVO = right ventricular outflow tract, LA = left atrium, MV = mitral valve leaflets, AV = aortic valve cusps, PV = pulmonic valve cusps.

vasive technique for assessing left ventricular size in the basal state. It can be easily performed on critically ill patients and is useful for day to day monitoring. An abnormal LHD after an acute myocardial infarction designates a higher risk group of patients who should perhaps be treated more vigorously. The method is useful as well for determining changes in left ventricular size after acute and chonic drug administration.

Dr. Ross: The newest and potentially perhaps most exciting method for cardiovascular exploration is ultrasound. This approach offers the opportunity of measuring absolute dimensions of cardiac structures as well as the dynamic motions of the cardiac chambers, valves, and great vessels. In addition, the recent development of multicrystal scanning ultrasound devices offers the promise of "dynamic pictures" of the heart, which eventually may rival in some ways those obtained by conventional cineangiography. Dr. Leopold will review certain recent advances in this field and discuss studies carried out in collaboration with Drs. Karliner and O'Rourke on the assessment of left ventricular performance in man by this technique.

Dr. George Leopold:* Single probe unidirectional echocardiography is now commonly employed in the non-invasive diagnosis of a variety of cardiovascular disorders, such as pericardial effusion,[31] mitral valve disease,[32,33] idiopathic hypertrophic subaortic stenosis,[34] left atrial myxoma,[35] and a wide range of congenital cardiac disorders. The conventional M-scan provides a time-motion display of various structures.

Another ultrasonic recording method which promises to yield significant information in the assessment of left ventricular anatomy and performance is the B-scan technique in which the ultrasound beam is swept along a single plane, the information being photographed from a storage oscilloscope. This method therefore provides a two-dimensional representation of the underlying cardiac anatomy rather than a time-motion plot. The plane most commonly chosen passes through the aortic root, mitral valve apparatus and body of the left ventricle (Figure 10). This is usually achieved by guiding the transducer along the third or fourth left intercostal space.

If desired, the returning echo information may be gaited to the electrocardiogram so that the heart is imaged only at a predetermined time in the cardiac cycle. The effects of cardiac motion are thereby negated. This technique has been termed "stop action" scanning.[36] A preliminary report by King[37] has indicated its usefulness in the estimation of left ventricular end systolic and end diastolic volumes. Alternatively, the recording may be made without gaiting (non-stop action) as proposed by Kikuchi.[38] With this technique the motion of all cardiac structures within the examination plane is recorded, yielding an image which is essentially an ultrasonic kymogram. Figure 10 shows such a scan along the long axis of the left ventricle of a patient with myocardopathy and dilatation of all cardiac chambers. The contours of the left ventricle, left atrium, and aortic root, as well as the positions of the mitral, aortic, and pulmonic cusps are easily appreciated. It is hoped that this technique will provide improved volumetric measurements of the individual chambers and possibly aid in detecting dyskinetic areas of the ventricular wall.

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*Associate Professor of Radiology in Residence, Director Division of Ultrasound.

A recent innovation in instrumentation, as proposed by Bom,[39] is the use of a phased array of transducers so that all portions of the scan may be viewed simultaneously, rather than using a storage oscilloscope. A prototype model of such an instrument, currently being evaluated in our laboratory, employs twenty closely spaced crystals in a single transducer head, which as in conventional B-scanning, may be oriented along any desired cardiac plane. To date we have employed the long axis plane described above as well as a transverse plane placed in the second or third interspace to observe the spatial orientation of the great vessels to each other. Although early attempts at volumetric measurements have been disappointing because of difficulty in resolving precisely the endocardial echoes, the qualitative evaluation of cardiac anatomy afforded is impressive. Abnormalities such as chamber enlargement, overriding of the aorta, mitral-aortic discontinuity, and septal hypertrophy are easily detectable in this real-time type of imaging which may be thought of as ultrasonic fluoroscopy. It is hoped that further technical refinements of this instrument will increase even further the scope of its applicability.

Although cross-sectional techniques promise much for the future, most clinical work still is performed with single transducer, unidirectional equipment. Assessment of left ventricular function is an important clinical application of this technique. However, as with other non-invasive methods, careful validation of the accuracy of this type of echocardiography by comparison with conventional hemodynamic-angiographic methods is essential. Ideally, such comparative studies should be carried out in the same patients.

Several studies have indicated that the ejection fraction (ratio of stroke volume to end-diastolic volume) determined by ultrasonic and cineangiographic methods correlate well with each other, although considerable scatter exists in individual patients.[40,41] Recently it was demonstrated in our laboratory that the mean rate of circumferential fiber shortening (mean Vcf) at the left ventricular minor equator, determined on a single plane cineangiogram, provides a useful measure of myocardial contractility.[42] To calculate mean Vcf, the extent of internal myocardial wall shortening from end diastole to end systole is divided by the ejection time; the value thus obtained then is corrected for end-diastolic circumference and the result expressed in circumferences per second (circ/sec). Normalization in this fashion permits comparison among patients. Since this angiographic measurement is derived from a chord drawn perpendicular to the long axis of the left ventricle, placement of an ultrasound beam in a similar plane should yield comparable results for mean wall shortening velocity (Figure 11). Indeed, reports of mean Vcf by echo have appeared with average normal values ranging from 0.92 to 1.45 circ/sec,[43,44] while mean

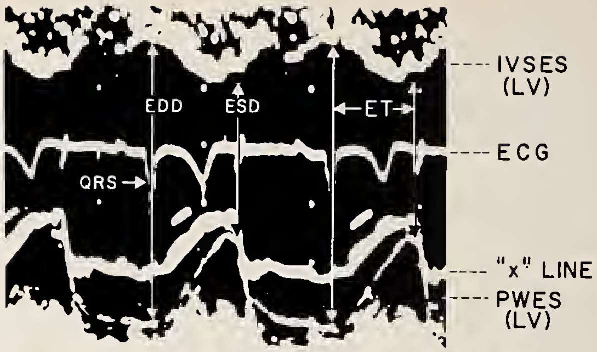

Figure 11.—Echocardiogram which shows the endocardial surface of the intraventricular septum (IVSES) and left ventricular posterior wall (PWES) as well as the "x" line. Although its exact identity has not been established, the "x" line is thought to represent echoes reflected from the mitral valve apparatus. Automatically incorporated into the display are the simultaneous electrocardiogram and time-distance markers. Distance is plotted on the vertical axis and time on the horizontal. End-diastolic dimension (EDD) between endocardial surfaces was measured along a vertical line drawn through the QRS complex. The systolic dimension (ESD) was defined as the smallest distance separating the endocardial surfaces of the septum and left ventricular posterior wall. Ejection time (ET) was defined as the length of time from the peak of the QRS complex to the maximum excursion of the left ventricular posterior wall, less 50 msec for the pre-ejection period when no appreciable fiber shortening takes place. (From Cooper RH, O'Rourke RA, Karliner JS, Peterson KL, Leopold GR: Comparison of ultrasound and cineangiographic measurements of the mean rate of circumferential fiber shortening in man. Circulation 46:914, 1972. Reproduced by permission of the American Heart Association, Inc.)

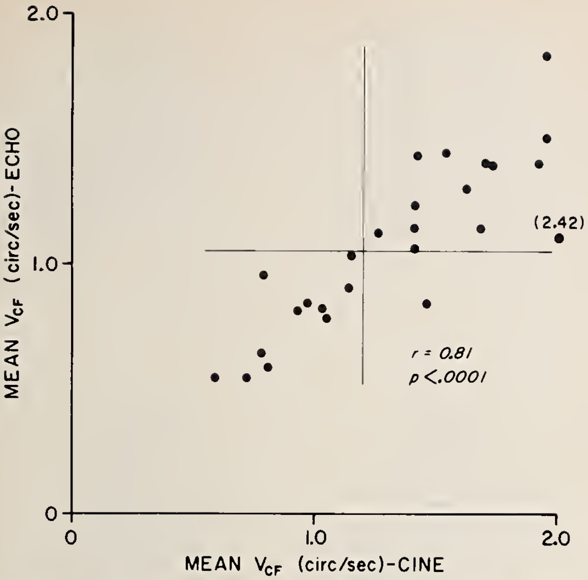

Figure 12.—Mean Vcf by ultrasound is plotted against mean Vcf determined by cineangiography. The crossed lines represent the lower limits of normal for each measurement (1.05 circ per sec for mean Vcf by echo and 1.20 circ per sec for mean Vcf by ciné). (From Cooper RH, O'Rourke RA, Karliner JS, Peterson KL, Leopold GR: Comparison of ultrasound and cineangiographic measurements of mean rate of circumferential fiber shortening in man. Circulation 46:914, 1972. Reproduced by permission of the American Heart Association, Inc.)

Vcf by ciné in the normal subject averages 1.50 circ/sec, with a lower limit of 1.2 circ/sec.[42]

Because of the wide range of mean Vcf by echo reported by others, we sought to compare echo and ciné measurements of mean Vcf in the same patients.[45] In 15 patients considered to have normal left ventricular function, the average mean Vcf determined by ultrasound was 1.29±0.23 (1 SD) circ/sec, while in 13 patients with reduced left ventricular performance this value was 0.75±0.16 circ/sec. The difference between these two values was highly significant. Values obtained by the echo technique showed a high degree of correlation with the results obtained by cineangiography and separated normal from abnormal left ventricular function in 27 of the 28 patients (Figure 12). The range of normal values was similar to that reported by McDonald and co-workers,[46] smaller than the normal range reported by Paraskos and associates,[44] and larger than that noted by Fortuin, Hood and Craige.[43] Reasons for the discrepancies among the various studies include differences in the plane of the left ventricle examined, alternative methods of normalization, and use of epicardial rather than endocardial surfaces of the posterior left ventricular wall. Since epicardial surface excursion is less than endocardial movement, owing to thickening of the left ventricular wall during systole, calculations using the former are subject to considerable error, the results being an underestimation of mean shortening velocity.

Whether or not internal shortening velocity measured in one plane in patients with wall motion abnormalities due to coronary artery disease can accurately characterize left ventricular function has been open to question. Accordingly, we recently examined the relation between mean Vcf determined by both the ciné and ultrasound techniques in 21 patients with abnormal wall motion.[47] The results indicated that the ultrasound technique was accurate in separating normal from impaired left ventricular function in all of the patients studied. Echo and ciné determinations of end-diastolic volume also showed a high degree of correlation in patients with wall motion abnormalities, although considerable volume overestimation by echo was observed in patients with widespread anterior akinesis or marked left ventricular enlargement.

Mean posterior wall velocity, especially at the left ventricular epicardial surface, is simple to measure by ultrasound. Further, it has been suggested that posterior wall velocity is sensitive to physiologic and pharmacologic interventions,[48] and it has been proposed as a measure of the inotropic state of the left ventricle.[49] In nine normal persons and in 39 patients with angiographically documented coronary artery disease, we compared mean endocardial posterior wall velocity by echo with ultrasound and cineangiographic calculations of ejection fraction and mean Vcf. In these patients we were unable to demonstrate a good correlation between mean posterior wall velocity, whether determined at the epicardial or endocardial surfaces, and mean Vcf and ejection fraction determined by cineangiography.[50] Moreover, of 25 patients with a reduced mean Vcf by echo, as described above, only three had a depressed mean endocardial posterior wall velocity. In comparison with other measures of myocardial performance, estimation of mean posterior wall velocity generally tended to overestimate left ventricular function. This finding may result from the absence of abnormal posterior wall movement in many patients with coronary artery disease as well as from the anterior motion of the whole heart during systole, which increases the recorded anterior movement of the posterior left ventricular wall.[46] Further, large day-to-day variations occurred in posterior wall velocity measured at the epicardial surface both in normal persons and patients with acute myocardial infarction. These observations indicate that ultrasonic measurement of mean posterior wall velocity provides an unreliable index of left ventricular performance.

Dr. Ross: These studies are illustrative, I think, of the progress being made in this rapidly developing field. As ultrasound methods gain increasing precision and are validated by direct comparison with established methods, we may look for increasing reliance on diagnostic ultrasound in the assessment of cardiac anatomy and function.

The final approach that we shall consider is the use of injected radioisotopes. The development of Anger type cameras has now allowed adequate visualization of the cardiac chambers and great vessels, and recently efforts have been made to apply this technique to the assessment of left ventricular function, and to study the myocardium in patients with coronary heart disease. We shall turn next to consideration of the use of ventricular imaging in the assessment of cardiac function. Drs. Karliner and Sobel have been interested in particular in the application of these methods in patients with acute myocardial infarction.

Radioisotope Angiocardiography

DR. JOEL S. KARLINER* AND DR. BURTON E. SOBEL:† Conventional cineangiographic methods for visualization of the chambers of the heart and the great vessels are of unequivocal value in patients with chronic cardiovascular disease and in defining the cause of certain acute disorders. However, they require cardiac catheterization and the rapid injection of radiopaque contrast medium under high pressure. These procedures are not without hazard, particularly in patients acutely ill with electrical or functional instability of the myocardium. Furthermore, although serial studies with contrast media are possible, frequent repeated cardiac catheterizations are potentially hazardous and are associated with some discomfort. Accordingly, considerable effort has been applied to development of other means, such as radionuclide angiocardiography, by which the cardiac chambers can be visualized. This procedure can be performed by peripheral venous injection of radionuclides and subsequent detection of the material with a gamma camera. It entails no significant risk, is virtually free from morbidity, and produces no hemodynamic perturbations.

Ventricular volumes can be quantified readily by radioisotope angiocardiography in experimental animals[51] and it has been shown that the method is applicable for cardiac visualization in patients with chronic cardiovascular disease.[52] Accordingly, we extended the technique to patients with acute myocardial infarction in a recent investigation designed to determine whether accurate assessment of left ventricular performance was possible in critically ill patients and to ascertain whether serial studies would provide useful information in such patients, thereby obviating the need for procedures utilizing contrast media.[53]

Radionuclide angiocardiography is performed by injecting a bolus of 7 to 15 mC of technetium-99m (sodium pertechnetate) through a Swan-Ganz catheter which has been floated into the pulmonary artery, or through an inlying peripheral venous catheter. Resolution is somewhat better when pulmonary arterial injection is utilized; however, acceptable results can be obtained by peripheral venous injection. The radiation exposure (0.06 to 0.16 rads per dose) is in the range of a conventional diagnostic x-ray and the radionuclide has a physical half-life of only six hours. An Anger-type scintillation camera is used for imaging the pattern of flow through the heart chambers. Sequentially obtained images are recorded and stored on magnetic tape along with the simultaneously recorded electrocardiogram. Both the stored video signal and the electrocardiogram are then replayed. With the use of a gating discriminator triggered by the electrocardiogram, images at either end-diastole or end-systole are summed and displayed on a storage oscilloscope. The cardiac silhouettes at each of these selected times are photographed directly, projected on a screen, and traced (Figure 13). Areas are determined by planimetry with appropriate corrections for magnification. These data provide information sufficient to calculate left ventricular end-diastolic volume, stroke volume (end-diastolic volume minus end-systolic volume), and ejection fraction (the ratio of stroke volume to end-diastolic volume).[53]

In 64 patients with acute myocardial infarction studied in the Myocardial Infarction Research Unit, left ventricular end-diastolic volumes determined by this technique averaged 101 ± 7 (1 SEM) ml/M², and it was elevated (>90 ml/M²) in 47 patients. Initial ejection fraction

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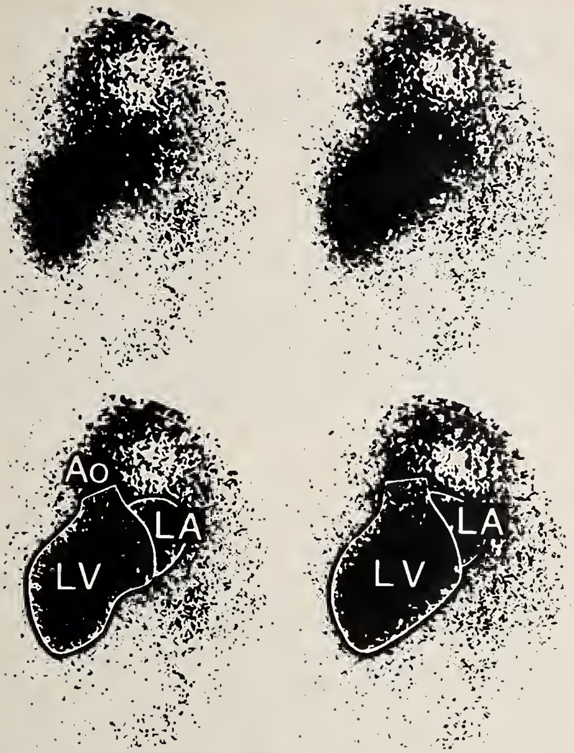

Figure 13.—End-systolic (left panel) and end-diastolic (right panel) images in the lateral projection obtained after peripheral venous injection of technetrium-99m in a patient with acute myocardial infarction. Anterior wall akinesis is apparent. In the bottom panels the silhouettes are outlined in order to depict the planimetered area used for volume and ejection fraction calculations. Papillary muscle images were not excluded from the planimetered areas. Since Sandler and Dodge have demonstrated that the radii in the postero-anterior and lateral projections are virtually identical, the formula for single frontal plane volume calculations proposed by these investigators has been applied to volume calculations in the lateral (L) projection: $V_L = 4/3\pi \times [D_L/2]^2 \times L_L/2$; $D_L/2$ = chamber radius in the lateral projection and L_L = the longest measured length in the lateral projection. The lateral chamber radius is derived from $D_L/2 = 2A/\pi\ L_L$; A = the planimetered area of the lateral left ventricular image. AO = aorta; LA = left atrium. (From Kostuk WJ, Ehsani AA, Karliner JS, Ashburn WL, Peterson KL, Ross J Jr., and Sobel BE: Left ventricular performance after myocardial infarction assessed by radioisotope angiocardiography. Circulation 47:244, 1973. Reproduced by permission of the American Heart Association, Inc.)

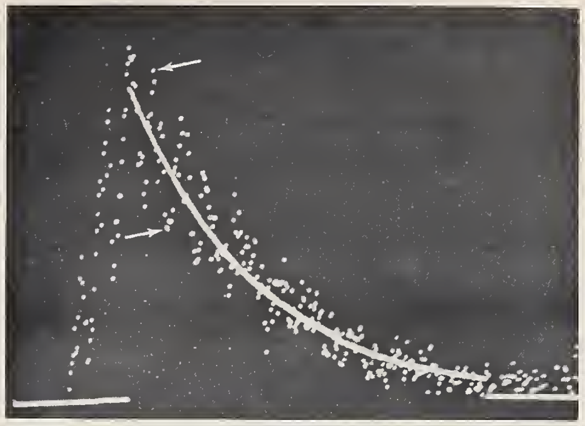

Figure 14.—Computer plot of time (abscissa) and counts (ordinate) during passage through the left ventricle of a radioactive bolus injected into the pulmonary artery. Each point represents total counts from "flagged" region corresponding to the left ventricle (corrected for background) for 0.04 sec. Cyclical change in counts is due to the beat-by-beat ejection of the tracer from the chamber. From the high and low values (arrows) per cardiac cycle, ejection fraction can be calculated. From the derived slope of the curve (heavy line) end-diastolic volume can be estimated.

averaged 0.38 ± .03 and was reduced (<0.52) in 58 (90 percent) of the patients. The extent of shortening of the diameter at the minor left ventricular equator determined from radionuclide angiocardiograms was decreased in 51 patients, and the reduction in fiber shortening was not consistently related to the site of infarction determined electrocardiographically. In 53 patients who subsequently recovered from the acute infarction, the initial ejection fraction averaged 0.40 ± 0.02, compared with 0.26 ± 0.07 ($p<0.05$) in 11 patients who died within one month.

Radionuclide angiocardiograms are useful in this setting also for detection of left ventricular wall motion disorders and mitral regurgitation. Forty-seven of the 64 patients with acute infarction exhibited abnormal wall motion detectable by the radionuclide technique and confirmed by radarkymography. Serial radionuclide angiocardiograms (obtained six hours to one month after onset of infarction) showed improvement of ventricular function in 30 of 55 patients. Left ventricular function assessed by this technique was unchanged in serial studies in 12 patients. Deterioration was apparent in 13 patients.

Additional quantitative methods for estimating left ventricular volume and ejection fraction are being investigated in a number of laboratories as well as our own.[54-56] Regions corresponding to the entire left ventricle are electronically "flagged" for computer evaluation, and a histogram of counts plotted against time is displayed for analysis (Figure 14). After correction for background contributions, the cyclical high (diastole) and low (systole) count values (Figure 14, arrows), which result from the beat-by-beat ejection of the labeled material from the left ventricle, are used to calculate ejection fraction (peak-to-valley/peak-to-zero level).

Dr. Ross: One of the most difficult areas of clinical investigation concerns the evaluation of acutely ill patients such as those with acute myocardial infarction. Dr. Sobel, could you expand a bit further on the application of this non-invasive measure of left ventricular function as it correlates with the size of an acute myocardial infarction?

Dr. Sobel: It is likely that a major determinant of impairment of ventricular performance after myocardial infarction is infarct size.[50] Accordingly, we compared infarct size estimated from analysis of serial serum CPK changes to ejection fraction determined by radionuclide angiocardiography in the same patients.

We have utilized a biochemical index to assess the extent of ischemic injury to the myocardium ("infarct size") in patients with acute myocardial infarction. This approach depends on mathematical analysis of serial changes in serum creatine phosphokinase (CPK) activity.[57] Since the amount of CPK released from the heart is related to the extent of ischemic injury, serial serum changes are used to estimate CPK released as a function of time. The analysis is based on the concept that changes in serum CPK activity reflect two competing phenomena: (1) release of CPK from myocardium undergoing necrosis, and (2) clearance of enzyme activity from blood, by mechanisms not yet thoroughly elucidated. When this technique was used to assess infarct size in patients we found that prognosis after myocardial infarction was closely related to estimated infarct size.[58]

The calculated infarct size in a group of patients with acute myocardial infarction is plotted against their ejection fractions, estimated by radionuclide angiography, in Figure 15. The data indicate that, in general, the severity of impairment of left ventricular function, reflected by the decrease in ejection fraction, was linearly related to infarct size. Scatter in the data is of course not surprising since ejection fraction is influenced also by numerous factors affecting preload and afterload.[53]

Thus, our experience with both of these non-invasive techniques in acutely ill patients indicates that radionuclide angiocardiography is extremely helpful in the assessment of left ventricular performance without injection of potentially hazardous contrast media in critically ill patients and that meaningful estimates of infarct size can be obtained readily by analysis of serial changes in serum CPK activity. Furthermore, it is becoming increasingly clear that infarct size is a major determinant of the severity of impairment of left ventricular function during the acute phase, and of prognosis in patients recovering from acute myocardial infarction.

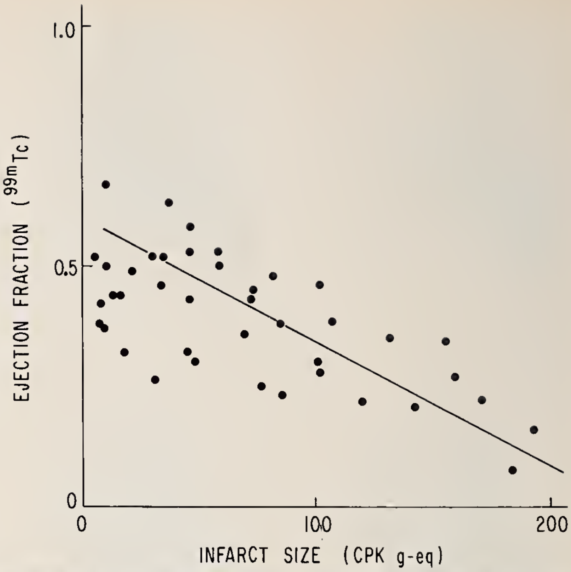

Figure 15.—Initial ejection fraction calculated from radioisotope angiocardiograms compared to estimated infarct size determined by the UCSD serial CPK method in 41 patients with acute myocardial infarction. The regression line (least squares method) best fitting these data is: $Y = -0.0032 \times +0.58$, $r = -0.73$, $n = 41$. (From Kostuk WJ, Ehsani AA, Karliner JS, Ashburn WL, Peterson KS, Ross J Jr, and Sobel BE: Left ventricular performance after myocardial infarction assessed by radioisotope angiocardiography. Circulation 47:247, 1973. Reproduced by permission of the American Heart Association, Inc.)

Intravenous Radioisotopes for Myocardial Imaging

Dr. Ross: Our final presentation concerns the use of a non-invasive technique for myocardial imaging which employs intravenously administered radioisotopes. Dr. William Ashburn will describe the current state of this new technique, which potentially is of great practical importance in the assessment of patients with coronary heart disease and acute myocardial infarction.

Dr. William L. Ashburn:* Ever since the observations by Carr and others[60-66] that certain intravenously administered radioactive substances such as cesium, potassium and rubidium concentrate in normal but not in infarcted myocardium in sufficient amounts to permit external imaging, investigators have continued to search for ways to pictorially demonstrate the extent and location of

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*Associate Professor of Radiology, Director, Division of Nuclear Medicine.

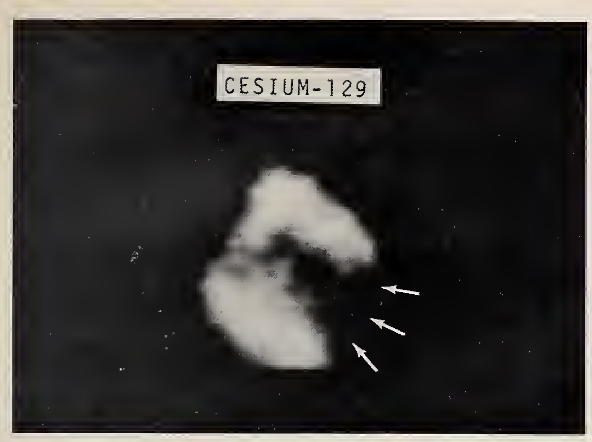

Figure 16.—Anterior ^{129}Cs myocardial image demonstrating "cold" deflect (arrows) in the area of known myocardial infarction in a 53-year-old man.

non-perfused myocardium by non-invasive radioisotope scanning using intravenous injections.

At present, the two most commonly employed radioactive agents for myocardial imaging are ^{129}Cs (32 hr. half-life) and ^{43}K (22 hr. half-life). Both of these radioisotopes are cyclotron-produced in limited quantities, although ^{43}K can be produced in large nuclear reactors. These radioisotopes emit gamma rays having approximately the same energy as ^{131}I (350-400 kev range), although ^{43}K also emits several higher energy photons the effects of which place special requirements on shielding and collimator design. Even so, useful images of myocardial uptake can be obtained with both rectilinear scanners and scintillation cameras.

Following the intravenous administration of ^{129}Cs, the maximum myocardial concentration of the tracer occurs at about 1 hour, at which time approximately 5 percent of the injected dose is present within the heart muscle. Identification of the heart outline is complicated by the concentration of ^{129}Cs in adjacent organs such as the liver, stomach, diaphragm and other soft tissues. However, some of the best images of infarcted myocardium, which appear as "cold" defects have been obtained with this radioactive agent (Figure 16). Because the rate of tracer clearance from normal myocardium is relatively slow, ample time for multiple view imaging is afforded.

By contrast, ^{43}K reaches maximum myocardial concentration within about 5 minutes following intravenous administration. The rate of clearance is relatively rapid with an effective half-time of approximately three to four hours in normal persons. Background radiation from adjacent soft tissues is somewhat less than with ^{129}Cs, but because of the higher energy photon contributions, some compromises in image resolution are necessary.

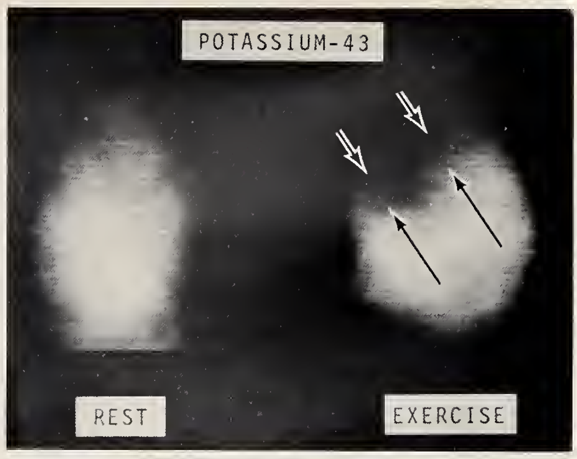

Figure 17.—Anterior ^{43}K myocardial images obtained at rest and exercise (see text). Large region of transient ischemia is suggested (arrows) on the study which followed a period of angina induced by treadmill exercise. Note also the increase in heart size with exercise.

Although ischemia, infarction and scarring each may be associated with clearly outlined areas of reduced myocardial concentration of the radioisotopes, these cannot ordinarily be distinguished by the appearance of the myocardial image. However, Zaret and coworkers[67] have taken advantage of the fact that ^{43}K is rapidly accumulated by normal but not by ischemic myocardium and have performed the imaging procedure immediately following a period of treadmill exercise stress to the point of angina or ST-wave changes, in order to maximally intensify the difference between normal and acutely ischemic tissue. A repeat study is then made on the following day while the patient is at rest and compared with the "exercise" image to note any apparent changes which suggest transiently ischemic regions of myocardium (Figure 17).

Since these procedures are non-invasive, considerable interest has arisen in attempting to apply such examinations in the evaluation of patients with coronary artery disease with or without previous myocardial infarction. So far, there has not been sufficient clinical experience with these techniques to determine their ultimate role in the diagnostic evaluation of patients being considered for revascularization surgery. Myocardial imaging is also being applied on an investigational basis in patients with acute myocardial infarction in order to determine whether the apparent size and location of the "cold defect" or any changing pattern during the early stages of the disease may aid in clinical prognostication and therapy.

Other radioactive substances have been mentioned as possible myocardial imaging agents and are being evaluated, by and large, in those laboratories having access to cyclotron produced radioisotopes. At present, ^{13}N (10 min. half life) labeled ammonia as well as other cyclotron produced radionuclides are being evaluated by Harper and coworkers[68] at the University of Chicago as well as by other workers. Thallium-203 is also being evaluated by this group, as well as by Lebowitz et al[69] at the Brookhaven National Laboratory. A variety of compounds labeled with ^{11}C and ^{125}I are being investigated by Poe and Eber[70] at UCLA as well as at a few other centers having cyclotrons. In addition, Bonte et al[71] at the University of Texas in Dallas have made a preliminary report concerning the use of oleic acid labeled with appropriate radioisotopes as potentially useful myocardial imaging agents.

Still another approach in myocardial imaging is receiving increasing attention. Since the original observations by Gorton et al[72] and Malek et al[73] that certain compounds appear to concentrate in infarcted myocardial tissue in sufficient quantities for external imaging, other workers have begun to search for suitable radioactive agents which might permit specific labeling of myocardial infarcts. In this category, ^{67}Ga citrate is being investigated by Johnston and coworkers[74] at the Clinical Center, National Institutes of Health, and ^{99}Tc-labeled tetracycline is undergoing evaluation by Holman and coworkers[75] in Boston. Another potentially useful compound appears to be ^{197}Hg labeled cysteinide.[76]

The results of these investigations indicate that it may become possible to satisfactorily image viable and/or infarcted myocardium as certain improvements in instrumentation and data handling techniques become available. It may be realistic to expect that we will be able in the not too distant future to distinguish between regions of healthy and under-perfused myocardium by non-invasive radioisotope imaging techniques.

Dr. Ross: In concluding this specialty conference, I should like to emphasize that some of the techniques described are still in the investigative stage, whereas others appear capable of providing clinically useful information about cardiac function at their current state of development. Within the latter category we may include the systolic time intervals, the plain radiographic and video methods, left ventricular imaging by radioisotopes, and standard diagnostic ultrasound. However, the potential for further improvements in the usefulness of each of these techniques as quantitative tools seems great, particularly exciting being the advances in ultrasonic methods. Rapid developments in radioisotope technology also offer the promise of better cardiac visualization, the ability to perform dynamic washout studies, as well as the possibility of detection of myocardial perfusion defects. It is not unreasonable to hope, therefore, that in the relatively near future it will become possible to reliably assess the cardiac patient by applying a combination of these indirect methods and thereby obviate the need for cardiac catheterization and angiography in many subjects.

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Medical Staff Conference

Refer to: Arthritis caused by viruses—Medical Staff Conference, University of California, San Francisco. Calif Med 119: 38-44, Sep 1973

Arthritis Caused by Viruses

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

Dr. Smith:* *It has been a tradition at this institution to have our chief residents give the Medical Staff Conference before their departure. Today, Dr. Wilkes will review what is known about the arthritides of viral origin and will also present some of his own research in this area.*

Dr. Wilkes:† Thank you, Dr. Smith. When we see acute arthritis, bacterial agents are considered in the differential diagnosis, but often little consideration is given to a viral cause. As is shown in Table 1, there are a number of viruses that can cause arthritis.[1,2] I would like to draw your attention especially to the viruses in the left hand column—hepatitis, rubella, mumps, and the group A arboviruses, chikungunya, o'nyong-nyong, epidemic polyarthritis, and sindbis. All these viruses are unequivocally associated with arthritis. Documentation of true arthritis caused by the agents listed in the right hand column is less well established. Smallpox may cause more of an osteomyelitis than a true arthritis, especially in children; and vaccinia, varicella, rubeola, and ECHO viruses have been implicated in case reports, but their etiologic role has not been fully substantiated.

Today we will concentrate on the viruses definitely known to cause arthritis and later consider the possibility of viruses as etiologic agents in rheumatoid arthritis. Why even discuss the arthritides caused by viruses? They are usually benign and self-limited diseases. Nevertheless, they are of interest because it is possible to confuse them with less benign forms of arthritis and because they suggest that some of the arthritides of unknown cause may have a viral origin. In addition, early diagnosis of a viral arthritis and recognition that this is usually benign and self-limited may spare the patient considerable anxiety, expensive laboratory investigation, and potentially hazardous forms of therapy.

Rubella

In 1906 Sir William Osler noted that arthritis was a complication of German measles or rubella.[3] Since that time a number of reports have shown that arthritis frequently accompanies rubella.[4-13] Although involvement of the joints is uncommon

TABLE 1.—*Viruses That Cause Arthritis*

Hepatitis	Arbovirus	Smallpox
Rubella	Chikungunya	Vaccinia
Mumps	O'nyong-nyong	Varicella
	Epidemic polyarthritis	Rubeola
	Sindbis	Echo

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*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine

†R. Michael Wilkes, MD, Chief Resident in Medicine

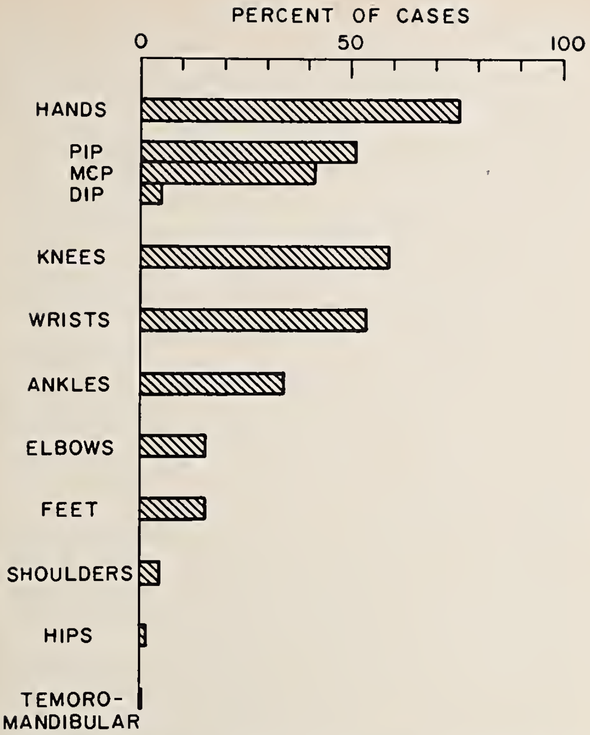

Chart 1.—Affected joints in 100 cases of rubella arthritis.

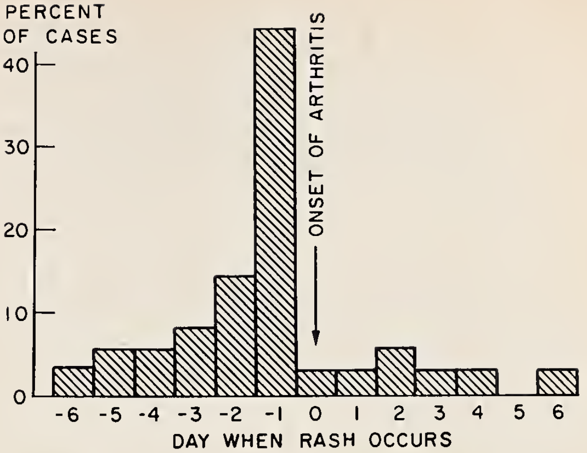

Chart 2.—The occurrence of rubella rash in relation to the onset of arthritis.

TABLE 2.—*Clinical Features of Rubella Arthritis*

Females: Males:: 9:1
Symmetrical polyarthritis
Joint distribution: Hands—75%
Knees—50%
Wrists—50%
Duration: 1½ weeks (range 2 to 51 days)
Recurrence: Rare
Rash: Usually precedes arthritis 1-2 days

TABLE 3.—*Laboratory Data in Rubella Arthritis*

Leukocyte numbers—normal or leukopenia
Sedimentation rate—elevated in 50 percent of cases
Rheumatoid factor—usually negative
ANA and LE preparations—negative
Joint fluid—15,000 leukocytes per cu mm
95 to 100% mononuclear
Rubella rarely isolated

in children, polyarthralgia and polyarthritis are such common manifestations in adults with natural rubella, especially women, as to be considered a typical manifestation of the disease. Surprisingly, rubella arthritis occurs nine times more frequently in women than in men (Table 2). Characteristically, several joints are involved, often symmetrically. Symptoms range from stiffness, which (much like rheumatoid arthritis) may be especially noticeable in the morning, to tenderness, swelling, limitation of motion, redness, and joint effusion. Occasionally, migratory polyarthritis occurs. In most cases the hands are involved and in more than half the knees or wrists are affected. The arthritis persists for one to two weeks but may last as long as two months. Recurrence is rare.

We have reviewed 100 cases of rubella arthritis. As is shown in Chart 1, the hands, especially the proximal interphalangeal joints and the metacarpophalangeal joints, were most frequently involved. They were affected in three-quarters of the cases. The knees and wrists were each affected in more than half the cases, then in decreasing order the ankles, elbows and feet; and rarely the shoulders, hips, and temporomandibular joints were involved.[4,6-10,12,13] An interesting feature which sometimes occurs is paresthesia in the hands, usually consisting of a numbness, tingling or a "pins and needles" sensation, which accompanies or follows the joint symptoms. This has been attributed to a carpal tunnel syndrome due to compression of the median nerve by swollen tendon sheaths.[5,9,10]

A rash often occurs with rubella and can be a clue that the accompanying arthritis is of viral origin. Small, irregular pink macules or papules usually begin on the face and then rapidly spread to the trunk and extremities.[4,7,9,10] In the majority of cases the rash precedes the arthritis by one or two days although it may precede or follow the arthritis by six days (Chart 2). The rash is transient, generally lasting only a few days.

Laboratory data are usually not helpful in rubella arthritis (Table 3). The white blood cell count is normal or slightly low, and the sedimentation rate is elevated in about half the cases, but

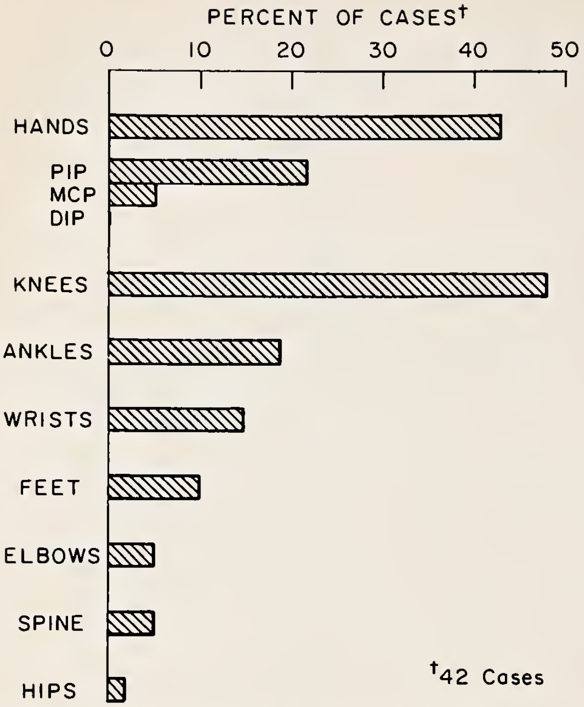

Chart 3.—Affected joints in 42 cases of rubella vaccine arthritis.

TABLE 4.—*Similarities and Differences of Rubella Arthritis and Rheumatoid Arthritis*

Differences	*Similarities*
1. Females>males	1. Self-limited
2. Symmetrical polyarthritis	2. No joint deformity
3. Metacarpophalangeal, proximal interphalangeal, knees, wrists affected	3. No rheumatoid nodules
4. Morning stiffness common	4. Rheumatoid factor rarely positive

TABLE 5.—*Clinical Features of Rubella Vaccine Arthritis*

Symmetrical polyarthritis
Most frequent joints—hands, knees
Onset—2 weeks after vaccination
Duration—4 days (1-14 days)
Recurrence—rare

rarely exceeds 50 mm. Tests for rheumatoid factor, antinuclear antibodies, and lupus erythematosus (LE) cells are nearly always negative.[6,9,10] Joint effusions of sufficient quantity for arthrocentesis are not common, but when aspiration can be done, analysis of the fluid shows about 15,000 white blood cells per cu mm, mainly mononuclear cells.[10,11] Rubella virus can rarely be isolated.[11]

Rubella arthritis has several similarities to as well as several differences from rheumatoid arthritis. I would first like to direct your attention to the similarities in the left hand column of Table 4. These similarities include a relatively high incidence in females; the fact that both are a symmetrical polyarthritis, most commonly involving the metacarpophalangeal and proximal interphalangeal joints of the hands as well as the knees and wrists; and that morning stiffness is common to both. On the right hand side of the table are listed the differences. Rubella arthritis is a self-limited disease, usually lasting one and a half weeks with no joint deformities, and there are no rheumatoid nodules. Only rarely is rheumatoid factor present. There has been one prospective follow-up study of patients with rubella arthritis and none showed any clinical manifestations suggesting rheumatoid arthritis after two to five years.[13]

Rubella Vaccine

Recently attention has been drawn to the arthritis that follows live rubella virus vaccination. Rubella vaccine rarely causes arthritis in children, but is often associated with polyarthralgia and arthritis in adults. When arthritis occurs, there is usually symmetrical involvement of several joints, especially the hands and knees (Table 5), beginning about two weeks following the inoculation of the vaccine and lasting on the average four days, although at times lasting as long as 14 days.[14-18] Occasionally recurrences of mild arthralgia occur up to a year after immunization, but recurrence of true arthritis is rare.

Women over the age of 25 have a higher incidence of arthralgias and arthritis. In a review of 350 seronegative women given rubella vaccine, only 7 percent under 25 years of age had joint manifestations whereas 31 percent over the age of 25 had arthralgias or arthritis.[15-17] In addition to age, endocrine factors may play a role in the development of rubella vaccine arthritis. This is suggested by the almost complete absence of joint manifestations in prepubescent children and also the low incidence in adult men compared with adult women. It has been suggested that oral contraceptives may reduce the incidence of arthralgias and arthritis,[14] although not all investigators have found this to be true.[18] Finally, arthritis is five times more common in women vaccinated within five days before or after the onset of menstruation than in those given the vaccine six to twenty-four days after the onset of the last menstrual cycle.[15] What the endocrine factors might be is not known.

In 42 cases of rubella vaccine arthritis that we have reviewed (Chart 3), the joints involved were principally the hands, especially the proximal interphalangeal joints, and the knees, with occasional involvement of the ankles, wrists and feet, and infrequently the elbows, spine and hips. No permanent joint damage occurs.[19] The pathogenesis of the joint manifestations that follow rubella immunization and that accompany natural rubella infection is not known. Possibilities such as viral invasion or an immune reaction have been proposed but not proved. Only infrequently has rubella virus been recovered from the synovial fluid in natural or vaccine rubella arthritis. Fortunately, the arthritis is generally a benign, self-limited disease with no long-term sequelae.

Viral Hepatitis

The association of arthritis with viral hepatitis was first noted in 1843 by Sir Robert Graves,[20] and this association has recently been re-emphasized.[21-32] Generally the arthritis precedes clinically apparent icterus by one to two weeks (Table 6), and in 86 percent of our patients this proved to be the case. Characteristically, there is a symmetrical polyarthritis, usually involving the proximal interphalangeal joints. Frequently there is morning stiffness, and the arthritis tends to last about three weeks, although sometimes it persists for as long as three and a half months.

As is shown in Chart 4, the hands, especially the proximal interphalangeal joints, are involved in 90 percent of the cases.[21-25,27,28] The knees are occasionally affected, but other joints are affected much less frequently. Skin reactions, especially urticaria, are common, usually occurring in the prodromal stage either alone or in association with the arthritis.[24,26] Angioneurotic edema and erythema multiforme may occur but are much less common than urticaria.[24,26,31,32]

Laboratory tests may be of help. However, when the patient presents with a polyarthritis, liver function tests are usually not obtained until after jaundice has appeared. Examination of the joint fluid has yielded varying results,[23,25,28] but generally several hundred to a few thousand cells are found, most of which are mononuclear cells. Hepatitis B antigen (HBAg), also known as Australia antigen or hepatitis-associated antigen (HAA), is almost always found in the serum in the acute stage.[24,25] In the few cases where joint fluid has been tested for HBAg, it has been positive, usually paralleling the levels found in the serum.[25] Serum complement studies are of interest (Chart 5). In patients with acute hepatitis arthritis, total hemolytic complement (CH_{50}), C3 and C4 are depressed, and high HBAg titers appear to be associated with low complement levels.[24,29] By contrast, in patients with viral hepatitis whose arthritis is in the convalescent stage or in patients without skin or joint involvement, the CH_{50}, C3 and C4 levels are generally normal or even elevated. It has been suggested that the correlation

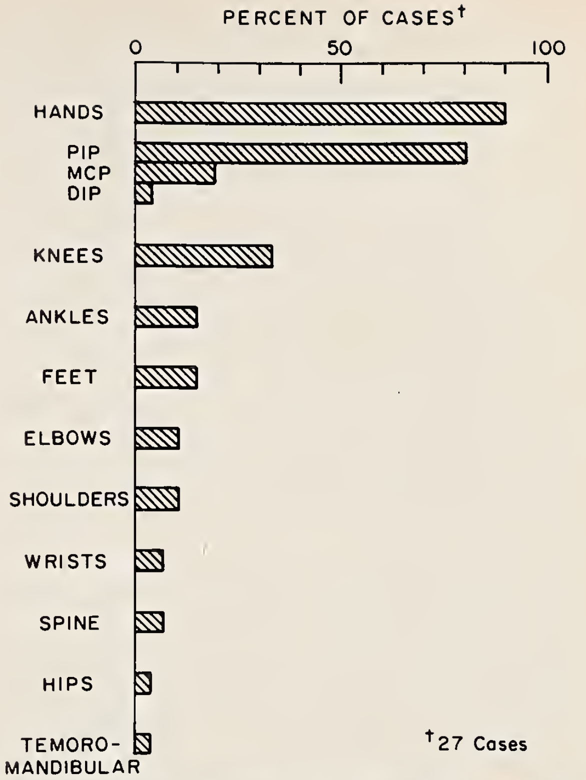

Chart 4.—Affected joints in 27 cases of hepatitis arthritis.

ARTHRITIS	CH_{50}	C3	C4	HBAg
ACUTE	⬇	⬇	⬇	+ +
CONVALESCENT	N or ↑	N	N	+
NONE	N or ↑	N or ↑	N or ↓	0 to +

N = Normal

Chart 5.—Serum complement and hepatitis B antigen (HBAg) levels in patients with acute and convalescent hepatitis arthritis and in patients with hepatitis but no arthritis.

TABLE 6.—*Clinical Features of Hepatitis Arthritis*

Precedes icterus 1-2 weeks
Symmetrical polyarthritis
Joint distribution—proximal interphalangeal 90%
Morning stiffness common
Duration 3 weeks
Urticaria common

of arthritis and urticaria with elevated HBAg and depressed complement levels may be due to a serum sickness like syndrome caused by circulating immune complexes. However, the possibility that the hepatitis virus may have a direct cytopathic effect on the synovium has not been excluded. Long-term complications of hepatitis arthritis have not been observed.

The arthritis of hepatitis may mimic that of serum sickness, lupus erythematosus, or rheumatoid arthritis, and the correct diagnosis may only be made when the jaundice becomes clinically apparent. Consequently, it is recommended that serum enzymes be obtained in all patients presenting with an unknown acute polyarthritis.

Mumps

Arthritis is a rare complication of mumps, occurring in about 0.5 percent of patients with that disease. Nevertheless, in view of the prevalence of mumps, this complication is worthy of mention. Men are affected five time more often than women (Table 7). Although mumps arthritis occurs between the ages of 5 and 50, it occurs most commonly in adults in their twenties.[33] The large joints are usually affected, especially the knees, shoulders, wrists, and ankles. Unlike many of the viral arthritides, especially rubella and hepatitis arthritis, the small joints of the hands are infrequently affected. The duration of the arthritis is quite variable, ranging from two days to three months, with most cases subsiding in two weeks. Swelling and tenderness of the parotid glands usually precede the arthritis by about ten days, but the enlargement may follow the arthritis or, on rare occasions, not even occur.[34] The diagnosis of mumps arthritis is not difficult when accompanied by parotitis. However, the diagnosis may be delayed when the arthritis precedes the parotitis and may not be made at all in the absence of parotitis unless viral titers are determined in acute and convalescent sera. Resolution of the arthritis occurs in all patients, with no residual joint damage.

TABLE 7.—*Clinical Features of Mumps Arthritis*

Males: Females:: 5:1
Age: Usually in 20s
Joint distribution: Knees, shoulders, wrists, ankles
Duration: 2 weeks (2 days to 3 months)
Parotitis: Usually precedes arthritis by 10 days

TABLE 8.—*Comparison of the Clinical Features of Chickungunya and O'nyong-nyong Arthritis*

	Chikungunya	*O'nyong-nyong*
Age	All ages	10 to 40
Sex	M=F	F>M
Fever	Elevated	Elevated
Rash	Morbilliform	Morbilliform
Onset	Sudden	Sudden
Joints	Multiple, large	Multiple, large
Severity	Severe	Mild to severe
Lymphadenopathy	Absent	Present

Arbovirus Infections

Arboviruses, so-called because they are arthropod-borne viruses, are frequent causes of arthritis in some parts of the world, such as Africa and Australia. *Chikungunya arthritis* occurs predominantly in Africa and was first described in Tanzania. Chikungunya arthritis affects all ages and is associated with a fever and morbilliform rash (Table 8). Again the rash is a clue to a viral cause. Multiple large joints are affected, but the distinctive features are its explosive onset and severity, the pain often so severe that morphine is required for relief.[35] Because of this, the name given the arthritis was the local term *chikungunya,* meaning "that which bends up." Joint involvement may last up to four months but there is no residual damage.

O'nyong-nyong arthritis is also caused by a group A arbovirus. It was first noted in Uganda and later in other areas of East Africa. It is very similar to chikungunya arthritis and is associated with fever, morbilliform rash, and a sudden onset affecting multiple large joints.[36,37] However, o'nyong-nyong arthritis tends to be milder than the preceding variety and is accompanied by cervical lymphadenopathy. No residual deformity occurs in this disease.

Rheumatoid Arthritis—A Viral Cause?

Thus, it is evident that arthritis can be caused by a number of viruses, including rubella, hepatitis, mumps, and some group A arboviruses. Is it possible that viruses play an etiologic role in rheumatoid arthritis? For many years there has been speculation that infection is an etiologic factor. Although this concept has received support from animal studies,[38-41] attempts to isolate bacteria and mycoplasma from humans with rheumatoid arthritis have been unrewarding.[42,43] Nevertheless, interest in a viral cause persists, because of the known association of viruses with acute arthritis and because of the realization that several human diseases, including progressive multifocal leukoencephalopathy[44,45] and subacute scle-

TABLE 9.—*Items in a Systematic Search for a Viral Cause in Rheumatoid Arthritis*

- SEROLOGIC SURVEY
- STANDARD VIROLOGIC TECHNIQUES
  - Co-cultivation
  - Hemadsorption
  - Hemagglutination
  - Interference
  - Staining for inclusion bodies
- NEWER VIROLOGIC TECHNIQUES
  - Heterokaryon or Cell fusion
- INTERFERON ACTIVITY
- ELECTRON MICROSCOPY
- IMMUNOFLUORESCENCE

rosing panencephalitis,[46,47] may be caused by recrudescence of latent viruses. For these reasons a study was undertaken at the National Institutes of Health to examine the possibility of a viral cause in rheumatoid arthritis.[48] How does one systematically search for a virus in a disease like rheumatoid arthritis? (See Table 9) Initially, a *serologic survey* is undertaken, and this is followed by standard virologic techniques. These include: *co-cultivation,* which depends upon a cell infected with a virus transmitting the virus to another uninfected and unrelated cell line of human or animal origin which can then express it; *hemadsorption,* which is the peculiar ability of red blood cells to stick to virus-infected cells; *hemagglutination,* where viruses released from infected cells cause red blood cells to agglutinate; *interference,* which depends upon the ability of a cell infected with a virus to prevent the multiplication of an exogenously added virus; and, finally, *staining for viral inclusion bodies.* If the foregoing techniques give negative results, then newer virologic procedures such as the heterokaryon or cell fusion technique can be employed, and tests for interferon activity and examination by electron microscopy and immunofluorescence can be undertaken.

Let us return to the first approach—the serologic survey. If a disease is caused by a known virus, then a serologic survey may be helpful in demonstrating an unexpectedly high incidence of antibodies or that antibodies are abnormally elevated in the patients. The role of measles virus in causing subacute sclerosing panencephalitis was suspected in part as a result of detecting extremely high antibody levels in these patients. Sera from patients with rheumatoid arthritis have been assayed for a variety of viral antibodies and the results compared with those obtained with sera from normal controls.[48] The frequency and titer of antibodies against rubella, measles, and mumps viruses, using the hemagglutination inhibition technique, were similar in patients with rheumatoid arthritis and normal subjects. However, a smaller proportion of the patients with rheumatoid arthritis were positive for cytomegalovirus, varicella-zoster, and herpes simplex viruses by complement fixation. This was found to be due to interference by rheumatoid factor of the complement fixation test. On retesting these sera after disruption of rheumatoid factor, the frequency and titer of these antibodies were found to be similar in the rheumatoid patients and the controls. Finally, the sera from the patients with rheumatoid arthritis were negative for HBAg. Thus, this serologic survey provided no evidence for an etiologic role of these viruses in rheumatoid arthritis.

Standard virologic techniques, such as co-cultivation, hemadsorption, hemagglutination, interference, and staining for inclusion bodies, have also failed to yield a virus from cell lines derived from over 100 joint fluid and tissue biopsy specimens, including rheumatoid synovia, nodules, and cartilage.[48] Thus, it can be concluded that many of our known viruses are not present in the joint fluids or tissues of patients with rheumatoid arthritis.

Recently, the heterokaryon or cell fusion technique has been employed to rescue a number of latent viruses not detectable by standard means.[49] In this procedure, a virus which cannot be demonstrated by standard techniques becomes apparent when the virus-infected cell is intimately fused with a different cell. By means of this technique, measles virus has been isolated from the brain cells of patients with subacute sclerosing panencephalitis[47] and a papovavirus has been found in neuronal cells of persons who had progressive multifocal leukoencephalopathy.[45] Employing the heterokaryon technique, no viruses were identified in synovial cells from patients with rheumatoid arthritis.

Tests for interferon activity have also been undertaken. In a trial using 14 rheumatoid joint fluid specimens, 12 showed interferon activity, as compared with only eight of 14 specimens from non-rheumatoid joints. In addition, the rheumatoid joint fluid specimens tended to have higher levels of interferon activity. Although this observation is consistent with an infectious process, other non-infection related stimuli, such as white blood cells which are present in higher numbers in rheumatoid joint fluid, can also induce an increase in interferon activity.[50] Finally, electron microscopy of rheumatoid synovial cells, obtained both from cell culture and directly from biopsy specimens, have been unrevealing.[51-53]

What do all these studies mean? First, they point out that the three most common acute viral arthritides in the United States—rubella, hepatitis and mumps—do not seem to be the cause of rheumatoid arthritis. Second, they indicate that the identification of a possible viral agent in rheumatoid arthritis will have to await the development of more sophisticated techniques.

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Important Advances in Clinical Medicine

Epitomes of Progress—Pathology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Pathology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pathology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, CA 94102

Inclusion Cell Disease (I-Cell)

THE ENIGMAS of mental retardation are slowly yielding to scientific inquiry. A form that has recently been clarified is inclusion cell (I-cell) disease which clinically resembles mucopolysaccharidosis or Hurler's syndrome. Charactertistically, numerous inclusions are found in cultured skin fibroblasts and there is an associated deficiency of several lysosomal hydrolases in the cells. Other lysosomal storage disorders are characterized by a deficiency of a single enzyme. In I-cell disease, the enzymes probably leak from abnormal cells and raise serum levels. Serum assay of these patients reveals an increase of β-D-glactosidase and β-D-glucuronidase, often to 50 times higher than normal values. Other lysosomal enzymes are also significantly elevated but to a lesser degree. Estimation of serum acid hydrolases provides an easy method to diagnose this condition.

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Immunoassays for Drugs of Abuse

ONE OF THE MORE recent adjuncts of immunochemistry has been its application to the detection of drug abuse. Immunological procedures have the unique capability of analyzing biological fluids directly; unlike the more conventional chromatographic or spectrometric techniques, these procedures require no sample pretreatment, extraction or concentration.

Current technology involves four immunochemical procedures: (1) An enzyme immunoassay technique (EMIT®), (2) a free radical assay technique (FRAT®), (3) radioimmunoassay, and (4) hemagglutination inhibition.

These methods are all based upon the same principle—the competitive displacement of labelled drug from a specific antibody-binding site by unlabelled drug present in the biological fluid. The procedures differ primarily in the nature of the label used to tag the drug molecule and the method employed to detect the label.

Assay kits for use of all four methods are available for the detection of opiates, including morphine, morphine glucuronide and codeine. In addition, the EMIT and FRAT systems have the capability of detecting amphetamine, barbiturate, cocaine and methadone. The first two methods, FRAT and EMIT, offer good sensitivity (300 ng per ml) with the unique capability of producing a quantitative determination on a single sample in one minute. Higher sensitivity requirements can be met by use of radioimmunoassay, which may routinely detect 60 ng per ml. Hemagglutination inhibition is a qualitative method with adjustable sensitivity and requires no instrumentation.

Single or small numbers of assays may best be performed by the EMIT system because of the immediacy of the result. This method and two others, FRAT and radioimmunoassay, can perform 600 to 1,000 analyses per day, using appropriate automated instrumentation.

RICHARD J. BASTIANI, PH D

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Cultured Skin Fibroblasts and Their Use in Genetic Counseling

FIBROBLASTS GROWING OUT from small biopsy specimens of skin can be maintained in culture for about 50 generations and have been used extensively in research on human infectious, metabolic and chromosomal diseases. Clinically, they may be used as an alternate tissue to detect suspected chromosomal mosaicism in (a) autosomal disorders with increased risk to future offspring and (b) sex chromosome disorders to determine the prognosis and therapeutic potentialities. All abortuses and stillborn or liveborn infants with congenital anomalies require chromosome study to rule out such etiologic factors and help in genetic counseling. In the first two cases, fibroblasts are the only tissue that can be obtained. Cultured cells may be useful in the diagnosis and counseling in inborn errors of metabolism. In the future, these cells may be useful to test a patient's response to drug therapy, drug side effects, ecological hazards, or dietary variation.

STEPHEN CEDERBAUM, MD

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Skeletal Scintiphotography and Metastatic Breast Carcinoma

SKELETAL SCINTIPHOTOGRAPHY using short-lived nuclides is the procedure of choice for detecting early metastatic bone tumors. This is of particular import in breast cancer patients, as the skeleton is the most frequent site of distant metastasis. Roentgenograms, serum alkaline phosphatase activity or a history of bone pain are all inferior to scintiphotography. Bone-seeking radionuclides localize in the skeleton and reflect its metabolic activity. Thus, while the scintiphoto locates the site of disease, it is nonspecific and should be accompanied by appropriate roentgenograms. In a cancer patient, abnormal scintiphotos without roentgenographic evidence of bone disease are considered presumptive evidence of early metastasis.

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Amniocentesis

AMNIOCENTESIS is becoming an accepted prenatal test to detect chromosome abnormalities, sex-linked diseases, and certain metabolic disorders in the fetus. It is a simple outpatient procedure which is performed at 14 to 16 weeks of gestation. We usually aspirate 15 to 20 ml of amniotic fluid from which cells are cultured and used for the chromosome or biochemical analysis. Results are available approximately four weeks later. Indications for amniocentesis include a maternal age of 35 years and over; a previous child with Down's syndrome or other chromosome anomaly; the mother or father is a known translocation carrier. The test may be used to determine sex when the mother is the carrier of a sex-linked disease and to detect a specific metabolic error if a previous child is affected with such a disease. The risk of abortion following the procedure is approximately 1 percent.

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Human Placental Lactogen (HPL)

HUMAN PLACENTAL LACTOGEN (HPL), also known as human chorionic somatomammotrophin, is a polypeptide hormone synthesized by placental syncytiotrophoblast. Circulating levels during the second half of pregnancy are in the 1 microgram per milliliter range, progressively rising from about 2 micrograms at 20 weeks to about 7 micrograms at 38 weeks. Consistently low levels throughout pregnancy or a sudden drop during the third trimester correlate strongly with fetal distress or neonatal asphyxia. During the first part of pregnancy, low levels are sensitive predictors of abortion. Technically, this is the simplest of radioimmunoassay procedures, and it is currently said to be the one most commonly done in Great Britain. HPL levels can also be detected by immunodiffusion in agar gel, but this technique is subject to greater variability.

Urinary estriol levels also reflect fetal and placental status, but the day-to-day variation may be wide. As the biological half-life of HPL is measured in minutes, it promptly reflects placental dysfunction or fetal distress.

JORGE FRANCO, MD

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"False Positive" Fluorescent Treponemal Antibody-Absorption Test Reactions

THE FLUORESCENT TREPONEMAL ANTIBODY-ABSORPTION (FTA-ABS) test was brought into the laboratory as a specific test for infection with Treponema pallidum. A variety of modifications of the original FTA procedure eliminated many of the nonspecific positive reactions found during preliminary trials. However, as the modified procedure began to be used in routine laboratories, several instances of "false positive" reactivity were reported.

The various diseases or clinical states in which such a positive reaction has reportedly occurred include systemic lupus erythematosus (SLE), pregnancy, vaccination and aging. One study of 250 nuns revealed three cases of definite positive reaction and five with borderline reaction, with no evidence of syphilis. An atypical fluorescent pattern has been reported in SLE, but not all laboratory personnel might recognize this.

Recently in our laboratory a higher than expected incidence of positive reactions was found in patients over the age of 50; many of the possible false-positive reactions were of low grade fluorescence. The fluorescence probably should be graded and reported as such, since many of the "false-positives" are of low grade fluorescence.

In any case, the FTA-ABS remains a useful and worthwhile confirmatory test, but must be used in conjunction with other laboratory tests, the patient's history and physical examination in establishing the diagnosis of syphilis.

STEBBINS B. CHANDOR, MD

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New (but Old) Hazards in Autopsy Pathology

VIRUSES ARE frequently unappreciated in the autopsy room. Such agents are difficult to see, culture, and identify, are often unsuspected clinically, and can cause the appearance of cryptic disorder in the pathologist. Particularly important are hepatitis and smallpox, but of increasing interest are conditions associated with the "slow viruses": Neurological afflictions, such as Jacob-Creutzfeld disease, are thought to be due to slow viruses that have recently been shown to be transmissible, have long incubation periods, and are uniformly fatal. There is a growing suspicion that at least some human neoplastic diseases, such as myelogenous leukemia and possibly certain sarcomas may be of viral cause, and thus potentially infectious. Tissues from such cases have heretofore been treated with disdain for infectious possibilities. It is frightening, however, to find that at least the slow viruses are not inactivated by death of the host or by subjecting them to formalin or to ultraviolet radiation. Autopsy room procedures should be re-examined, scrupulous technique employed, and soiled materials autoclaved or otherwise sterilized for personnel safety.

W. JANN BROWN, MD

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Estriol Assays to Assess Fetal Status

Among tests used to monitor fetal well-being in complicated pregnancies, estriol assays appear most useful. Estriol production rises a thousandfold from ovulation until term, and in late pregnancy depends overwhelmingly upon normal fetal as well as placental function. Hence, fetal distress will result in decreased estriol excretion even in conjunction with normal placental function. A normal pattern of 24-hour urinary estriols is regarded as a useful indicator of fetal well-being in pregnancies complicated by "postmaturity," intrauterine growth retardation, fetal death, hypertension and toxemia, and diabetes, if estriol is measured reliably, serially, and with appropriate frequency, particularly in diabetic women. Estriol excretion may be misleading in Rh-isoimmunization, and in anencephaly, as well as in cases with maternal corticosteroid and ampicillin therapy and impaired renal function. Falsely low estriol values may be due to mandelamine treatment, incomplete urine collection, and laboratory errors. Cumbersome and often inaccurate 24-hour urine collections may soon be obsolete when plasma estriol radioimmunoassays become generally available.

Uwe Goebelsmann, MD

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Fibrin Split Products

Coagulation systems are activated *in vivo* in association with a variety of specific diseases. The presence in plasma of fibrin split products is one of the most sensitive indicators of an *in vivo* coagulative process (consumption coagulopathy). Fibrin split products are usually demonstrable in the disseminated forms of combined platelet and fibrinogen consumption characteristic of bacteremia, metastatic carcinoma and obstetric complications, as well as in more localized forms associated with venous thrombosis and tissue trauma. These forms of consumption coagulopathy appear relatively amenable to anticoagulation therapy with heparin. Fibrin split products are also usually demonstrable in consumption coagulopathy in which platelet consumption is dominant, as in arterial thrombosis, thrombotic thrombocytopenia purpura, hemolytic-uremic syndrome and vasculitic syndromes. These appear to be therapeutically more amenable to inhibitors of platelet function and the inflammatory reaction.

Fibrinogenolysis, the cleavage of fibrinogen—not fibrin—may occur secondary to consumption coagulopathy or may be independent. In this latter event, which appears to be associated with primary activation of the plasmin system, there is no platelet consumption, and fibrinogen split products are found in the plasma.

Hence with appropriate techniques that are now just emerging, it appears possible to detect *in vivo* coagulative processes as well as primary fibrinogenolytic processes. Diagnosis and management require rational integration of clinical and laboratory data.

Thomas S. Edgington, MD

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Carcinoembryonic Antigen (CEA) in Clinical Diagnosis

Carcinoembryonic antigen is a tumor-associated antigen that may prove useful in clinical diagnosis and management of malignant disease of the gastrointestinal tract and, to a lesser extent, the lung and breast. Low concentrations present in the plasma of normal persons are usually increased in patients with such diseases. The frequency of positivity and concentration correlates with the extent of tumor, being low in small nonmetastasized colonic carcinoma (40 percent positive in Dukes Stage A) and high in patients with metastatic tumor (90 percent in Dukes Stage D). Plasma CEA is elevated in more than half of patients with operable tumors (Dukes Stages A and B). The decline in plasma CEA following resection of carcinoma of the colon is of prognostic value. However, because of the complexity and differences between assays, results should be interpreted within the guidelines established by the laboratory.

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Serum Alkaline Phosphatase Isoenzymes

IT IS NOW WITHIN the capability of laboratories to identify and even to quantitate each of the alkaline phosphatase (AP) isoenzymes in sera. A variety of methods attempt to accomplish this with varying degrees of success. Procedures include the use of "selective" inhibitions (by heat, urea, L-phenylalanine) or a variety of electrophoretic methods (starch gel, acrylaminde gel, agarose, cellulose acetate). Some of these are less accurate discriminators for all sera. One reason for the inaccuracies may be the moderate diversity occurring with bone AP and to a lesser extent liver AP. This causes the alkaline phosphatase isoenzyme system to be more complex than the LDH system. Thus, each person probably belongs to a particular "set" with respect to his alkaline phosphatases.

One of the more successful analytical procedures utilizes electrophoretic separation in acrylamide gel. Discrimination of bone AP is enhanced by observing its inactivation by heat (56°C for 10 minutes), or urea in a second gel. Demonstration of placental AP requires a special procedure. Five tissue-derived AP can be demonstrated in serum. These are contributed by (1) liver, (2) bone, (3) intestinal mucosa, (4) bile, and (5) placenta. Most normal adult sera contain only 2 AP isoenzymes, namely, liver AP and bone AP, with the former predominating.

Normal children, especially adolescents, show an increased bone isoenzyme. In adults, the increased bone AP is found in Paget's disease, during bone fracture repair, and in hyperthyroidism.

Intestinal AP occurs normally in about 1 percent of the population in association with blood type O or B secretors. Intestinal AP can occur in cirrhosis, irrespective of blood type.

Bile AP is an abnormal constituent. It appears to reflect biliary stasis and therefore does not always occur when the liver AP is increased. In cirrhosis, bile AP can occur with a normal level of liver AP. Bile AP may be more difficult to distinguish when cellulose acetate or agarose electrophoresis is used, since this isoenzyme migrates close to the liver AP in those systems.

Placental AP can be demonstrated during the last trimester of pregnancy and for a short period after parturition. This isoenzyme is extremely resistant to heat inactivation. Neither bone nor liver AP appears elevated at this time.

The fractionation of alkaline phosphatase will probably find its greatest usefulness in identifying the cause of a moderately elevated total serum alkaline phosphatase (when other laboratory measurements are normal) in children and adolescents suspected of liver disease, and possibly in certain cases of pregnancy.

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Nitroblue Tetrazolium Test as Evidence of Bacterial Infection?

THE ABILITY of a patient's leukocytes to reduce nitroblue-tetrazolium (NBT) is the basis of a fairly widely used although still controversial means of identifying bacterial infection in patients with fever of unknown origin. Claims of usefulness are balanced by reports of poor results, and the controversy continues. Malignant lymphomas have been associated with negative results in some laboratories, but one group has found that the NBT test frequently was positive in patients with Hodgkin's disease or malignant lymphoma in the *absence* of complicating bacterial infections.

Recent reports give reason for withholding full acceptance of the test:

- Ten to 20 percent of "negative" tests are invalid;
- Negative results are common during antibiotic medication even when severe infection persists;
- The effects of steroid therapy on test results remain controversial.

Authorities still disagree on a number of important points concerning the technique to be used. Unless it can be refined and methods of control established, the usefulness of the test as a routine procedure in the recognition of bacterial infections will remain questionable.

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Detection of Drug Abusers by Urine Screening

To detect drug abusers for purposes of individual treatment, for identification of "epidemic carriers," and for prevention of various employee risks, mass urine drug screening has become widely applied. Many objections have been voiced on the grounds of invasion of privacy, the specimen and result mixup probabilities, and technical error rates.

Methodological approaches include thin layer chromatography (TLC), ultraviolet spectroscopy (UV), gas chromatography (GC), free radical assay technique (FRAT®), and enzyme immunoassay technique (EMIT®). Sensitivity levels are one key point upon which the likelihood of false positives or false negatives rests. In terms of consequences, the difference between reporting a positive urine glucose or morphine is extreme.

One 1972 urine drug screening quality control program tested ten California laboratories and found average results of: (1) correct, 40 percent; (2) false positive, 42 percent; (3) false negative, 48 percent; and (4) misidentification, 10 percent. It seems unlikely that any mass screening program now operative is performing at an acceptable level of competence.

Considering the cost of doing these programs well and the potential consequences of error, we have proposed a moratorium on all such programs in clinically well individuals unless more fail-safe methods become available.

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Use of Packed Red Blood Cells for Transfusion

Recent advances in transfusion therapy demand the use of specific components and derivatives rather than of whole blood. Increasing requirements for Factor VIII as cryoprecipitate or lyophilized concentrate, prothrombin complex (Factors II, VII, IX, and X), and platelet concentrates tax or exceed the available supply of volunteer donor blood. Most blood units must therefore be fractionated, leaving mostly packed red blood cells for transfusion purposes.

Transfusion serves two purposes: first, the replenishment of the oxygen-carrying capacity by the addition of red blood cells; and second, the restoration of the intravascular volume in an acutely bleeding patient. Recent work has clearly demonstrated the efficacy of volume replacement by balanced electrolyte solutions, thus reducing the amount of blood required for transfusion and also making possible the predominant use of packed red blood cells for the replacement of the oxygen-carrying capacity. Experience has shown the real feasibility of administering the first two units of blood required by any patient as packed red blood cells, and at least every other unit thereafter. At least 80 to 85 percent of all blood should be used as packed red blood cells. When absolutely required, "whole blood" may be synthesized from packed red blood cells and fresh frozen plasma, supplemented by platelet concentrates as necessary.

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EDITORIAL

Satisfactory Care at Low Cost

A LITTLE-PUBLICIZED Technical Report from the Department of Health, Education, and Welfare entitled "The Cost of Standard Medical Services under Alternative Delivery Systems" contains data which clearly show that the cost of a "physician encounter"—that is, a visit where a patient is seen by a physician—is least in a private practice situation, greater in so-called prepaid health plans such as the Health Maintenance Organizations (HMO) prototypes and greatest in Neighborhood Health Centers such as those funded by the Office of Economic Opportunity. The differences in the cost as they are reported are substantial enough to be significant, even though the services may not be precisely comparable.

Findings such as these are difficult to reconcile with the highly publicized thesis that federally subsidized HMO's are *the way* to reduce the cost of medical care. The evidence seems clear enough. Since the cost of the standard service in these plans is significantly higher, the goal of reducing costs can be achieved only by curtailing the number of times the services are rendered. This method of cost containment is not likely to be satisfactory either to patient or physician, since the patient may be deterred from securing needed services and the physician may be deterred from rendering the quantity and quality of services he believes the patient should have. Yet on the other hand it is well worth noting that in the private practice situation both patient and physician must be satisfied with it or the relationship simply will not continue. The DHEW study would suggest that this is care at low cost and we would suggest that is satisfactory as well.

In summary, then, it might just be true that private care in a physician's office is the most economical way to render satisfactory care. The evidence in the cited report supports this possibility. And if it is so, then it would seem rational for the government to try to encourage rather than discourage, strengthen rather than weaken what has been shown by its own technical study to be the least expensive way to render satisfactory care.

—MSMW

Coccidioides in the Soil and the Meninges

COCCIDIOIDOMYCOSIS, we are reminded in this issue of CALIFORNIA MEDICINE, sustains itself as a disease of particular interest in the north-south expanse of California (as well as Arizona and elsewhere) and the treatment of the disseminated form of the disease remains a rigorous, sometimes alarming challenge.

It is ironic that Ishi, "the last wild Indian of North America," who was movingly biographed by Theodora Kroeber, had survived the depredations and feral hazards that claimed all his fellow Yahi tribesmen and women only to die in San Francisco of the disease of civilization, tuberculosis. It is likely that Ishi and others of his nation, peregrinating among the slopes, cliffs, gorges and streams of the region identifiable now as Tehama County, were exposed to Coccidioides immitis and that some of them had been infected with the fungus. Perhaps their remains reinoculated the soil with the fungus, though such passage through a mammalian host is not essential to maintenance of this "pathogenic saprophyte" in nature. Ishi himself may have survived such an infection but there was little likelihood that it contributed to his death in 1916, as the postmortem confirmation of tuberculosis was made by Dr. Jean V. Cooke, an early investigator of coccidioidal granuloma.[1] Excavations conducted during studies on the Yahi (Yana) and earlier Indian inhabitants of California have led to coccidioidal infection of archaeologists and to the recovery of C. immitis from the soil. This fungus has thus been revealed far north of the traditional San Joaquin Valley into Yolo, Butte and Tehama counties (Werner and Pappagianis, elsewhere in this issue). Other deliberate disturbances of soil occupationally or by children at play have made it possible to pinpoint sources of infection.

That C. immitis is not confined to the hot central valley and desert regions was shown by the fascinating occurrence of cases of coccidioidomycosis and isolation of the fungus from the soil in the area of Pacific Beach in San Diego county.[2] While several of these outbreaks have been tied, as have individual cases, to activities related to disturbance of the soil, it is likely that the usual individual patients coming to a physician's attention have had no overt dusty experience which might arouse suspicion of "coccy" in the clinical history. Virtually all such patients, however, will have had a period of residence or travel in the endemic area and only rarely will exotic infections occur as described by C. E. Smith, who transported spores of C. immitis on cotton bolls from Pumpkin Center, Kern County, to San Francisco.[3] Exportation of San Joaquin Valley cotton more recently led to lethal coccidioidal infection in a man in North Carolina.[4]

Recognition of new areas in Northern California and additional sites elsewhere in the state frequently raises the question whether C. immitis has escaped from its erstwhile confines in the state. It is more likely that the presence of the fungus is being divulged by dislodgment of soil by a variety of excavation projects. With the recognition that infections occurred as far north as Tehama county, however, it seems wise to maintain an open mind and suspect "coccy" if the appropriate clinical picture presents itself. Here, alas, is a diagnostic problem, for an "atypical" clinical picture has often led to misdiagnosis even by physicians in the endemic area familiar with the usual manifestations of this disease. An important case in point is the deceptive presentation of coccidioidal meningitis by a change in personality or mentation and without a recognized proximate occurrence of a febrile respiratory illness.

Upon diagnosis of coccidioidal meningitis, the physician and the patient may be confronted with a sense of desperation. Notwithstanding the toxicity of amphotericin B, however, numerous patients with coccidioidal meningitis have survived five to fifteen years since the advent of this antibiotic. Some of these likely represent real "cures" of a disease that generally used to run its lethal course within one year. The exploration and development of therapy of coccidioidal meningitis with amphotericin by William Winn and Hans Einstein and their colleagues led ultimately to the recognition that the cisternal route of administration of amphotericin B was the preferred method of treating coccidioidal meningitis, which generally is confined to the basilar areas of the brain.

The cisternal approach was adopted when it was recognized that administration of the usual suspension of amphotericin B into the lumbar intrathecal area generally led to arachnoiditis and radiculitis, though a very few patients have been successfully treated by this route. The administration of amphotericin B—never undertaken lightly—into the cisterna magna, nevertheless has been applied in many patients, with repeated administration of amphotericin by this route. Winn reported on 31 patients, most of whom were treated with cisternal amphotericin, some with 100 to 200 cisternal punctures.[5] One of Winn's patients received cisternal amphotericin therapy (247 injections) over a period of 57 months only to die of massive hemorrhage from a sclerotic middle cerebral artery. At necropsy there were no local changes in the cisternal area that might have been ascribed to the cisternal injections. Nevertheless, Keane in this issue of CALIFORNIA MEDICINE properly points out the hazards associated with cisternal puncture, which can be lethal, and would reserve it for use only by the well trained and only when therapy is essential.

The experience of Winn and Einstein and others has provided solid evidence of the benefits of cisternal therapy of coccidioidal meningitis. However, the response of patients to repeated cisternal puncture is variable, with nausea and vomiting, occasional seizures, or neurologic defects involving the cranial nerves resulting from such injections. Severe headache may develop despite the use of anodynes, and in time a sense of terror may develop in a patient undergoing this form of therapy. The application of the Ommaya subcutaneous reservoir and ventricular catheter in the treatment of more than 50 patients with coccidioidal meningitis has suggested that this alternative may be useful in some cases; but it, too, is fraught with problems, including headache and neurologic effects from intraventricular injection of amphotericin. Secondary bacterial infection, particularly with Staphylococcus epidermidis, is a frequent complication.

It is therefore an exciting and welcome development reported by Glynn, Alazraki and Walsh in this issue that an acceptable lumbar intrathecal method of administration may obviate the complications associated with the cisternal or intraventricular treatment. Thus, with the use of hyperbaric glucose mixed with amphotericin B and with the patient tilted to achieve rapid movement of the amphotericin into the basilar cisterns, an important innovation may be available for the treatment of coccidioidal meningitis. Glynn and his coworkers point out that they did not assay for amphotericin B in the cisternal fluid, though the prompt cephalad movement of the bolus of hyperbaric I^{131}-serum albumin injected simultaneously with the amphotericin was documented.

It is a fair presumption that the amphotericin did leave the lumbar region or at least was sufficiently dispersed, as repeated injections have not led to the usual arachnoiditis associated with lumbar injection of amphotericin. Furthermore, clinical and laboratory evidence of improvement of the patient suggests that amphotericin reached the base of the brain in effective concentration. However, proof of such movement must be sought by assaying the cisternal fluid for amphotericin, preferably by employing radio-tagged amphotericin B.

The hyperbaric glucose-amphotericin B method has been applied in at least three other patients, one of whom (a physician) did not tolerate it by this route, but he was also intolerant of even small doses by cisternal or lumbar routes without the hyperbaric glucose. Two other patients have tolerated the hyperbaric glucose-amphotericin mixture by lumbar route extremely well, though the ultimate resolution of meningitis in one of these patients remains to be achieved.

In the past it has been essential to refer patients with coccidioidal meningitis to physicians uniquely prepared to carry out the cisternal therapy or to implant the Ommaya device. This has led in many instances to economic hardships, displacement of patients from their homes or difficult transportation problems not to mention the attendant clinical problems. It will of course be essential to make the diagnosis of coccidioidal meningitis promptly in order to provide the best opportunity for success with the intralumbar hyperbaric glucose-amphotericin B method. It should nevertheless be applicable by physicians competent in the performance of the usual lumbar puncture. To reduce the arachnoidal reaction, Einstein and Glynn have recommended substitution of depot methylprednisolone acetate in place of hydrocortisone to precede the intrathecal injection of the amphotericin B suspension, and they have emphasized the need to inject the medications in a volume precisely equivalent to that of the cerebrospinal fluid withdrawn.

The method must still be considered as an investigative procedure until there has been clear demonstration of movement of amphotericin to the cisternal area and additional experience is gained in other patients to justify its substitution for the cisternal or ventricular therapy. Appropriate close monitoring of glucose, protein, cells and complement fixation titer of the cerebrospinal fluid will continue to assist in assessment of progress of therapy.

While new and less toxic antifungal agents are needed (and immunotherapy with transfer factor may assist in this), improved application of the sole currently available agent, amphotericin B, will allow easing of some of the difficulties associated with treatment. Thus, assay of the sensitivity of a patient's own strain of C. immitis may be helpful in treating with the minimum necessary dose of amphotericin. Unfortunately, isolation of C. immitis from the cerebrospinal fluid has been erratic and infrequent. Yet the very low level of cholesterol (0.4 mg per 100 ml) normally present in the fluid should minimize interference with the antifungal activity that amphotericin B encounters in the blood plasma.

Disseminated coccidioidomycosis and especially meningitis provide a challenge but this has now been met successfully in enough patients to provide encouragement to those in whom these complications develop.

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Non-Invasive Cardiology, A New Horizon

AS A RESULT of rapid and spectacular progress over the past three decades in techniques and procedures for the direct diagnosis of heart disease and evaluation of cardiocirculatory function, the specialized science of cardiac catheterization has become relatively well defined and standardized. During the last five years, increasing attention in cardiovascular methods has turned to the development of improved non-invasive techniques which provide reliable information combined with patient safety. The excellent specialty conference presented by John Ross, Jr. and his colleagues of the Cardiovascular Division at UCSD in this issue of CALIFORNIA MEDICINE focuses attention on the value and limitations of the principal advancements which have been achieved recently, as well as prospects for future progress in non-invasive methods for the assessment of cardiac performance.

First, the simultaneous recording of the phonocardiogram, external carotid arterial pulse and the electrocardiogram allows indirect measurement of the cardiac systolic time intervals (STI) of pre-ejection period (PEP) and left ventricular ejection time (LVET) which provide useful estimates of cardiac function. Since the PEP lengthens while LVET shortens when cardiac contractility is depressed, an increase in the PEP:LVET ratio distinguishes most patients with moderate to severe heart failure from normal persons. However, as emphasized by O'Rourke, resting STI do not reliably detect mild to moderate cardiac dysfunction in single patients because STI are sensitive to several hemodynamic variables in addition to contractility. On the other hand, serially obtained STI are usually of value in evaluating changes in cardiac function in response to an intervention, and also in patient follow-up. Also, we have established regression equations for normal STI during maximal treadmill exercise and have found divergence from these values to be useful in identifying patients with coronary heart disease.[1]

Second, radarkymography constitutes the analog recording of the motion of selected portions of the external cardiac wall by electronic video-tracking of the border of the heart during image intensification fluoroscopy. Quantification of segmental ventricular contraction by this technique has been valuable in the detection of dyssynergy in coronary heart disease and in determination of the acute response of regional movement to pharmacologic intervention. For evaluating epicardial wall motion the method possesses several advantages over the other objective atraumatic techniques including roentgenkymography, electrokymography, apexcardiography and kinetocardiography. In our experience with radarkymography,[2] its major limitation has been difficulty with equipment function. Peterson and Ludbrook described an improved modification of this method, the video dimension analyzer, for the study of ventricular diastolic filling patterns and assessment of the extent and velocity of external myocardial shortening.

Third, estimation of left ventricular volume is provided by a special measurement approximating external left heart dimension on a supine frontal chest roentgenogram taken in a controlled manner. Crawford described the application of the method after acute myocardial infarction in the serial evaluation of cardiac performance and in predicting survival and chronic heart failure. Also, this radiographic-obtained dimension can be used to detect changes in left ventricular volume induced by acute and chronic drug administration.

Fourth, the most important new examining technique in cardiovascular medicine is echocardiography. By providing acoustic images of pulsed ultrasound reflected from the interface of different media, the echogram measures dynamic movement of heart chambers and valves, gives absolute dimensions of cardiac structures, and quantitates hemodynamic and mechanical performance characteristics of the heart. Both unidirectional time-motion recordings and two-dimensional one-plane scans of the heart are provided by the single probe echographic method now being widely employed in clinical cardiology. This instrument has rapidly become an indispensible tool in the reliable diagnosis of pericardial effusion, mitral valve disease, idiopathic hypertrophic subaortic stenosis (IHSS), left atrial myxoma and several types of congenital heart disease. We have been particularly interested in its use in evaluating IHSS,[3] mitral valve prolapse[4] and interventricular septal motion in coronary heart disease.[5] With regard to ultrasonic assessment of cardiac contractility, Leopold and coworkers indicated that mean rate of circumferential fiber shortening (mean V_{CF}) is a helpful index, whereas mean posterior wall velocity is an unreliable measure. Also, we have found echographic-determined mean V_{CF} to be valuable in identifying subclinical cardiomyopathy.[6] Concerning future innovations, Leopold described preliminary work with multicrystal scanning ultrasound which affords three-dimensional representation of cardiac structures.

Finally, the recent availability of the Anger gamma scintillation camera, capable of recording wide-field radioisotope images over the precordum, has stimulated the development of radionuclide angiocardiography[7] and its extension to non-invasive evaluation. Thus, following peripheral venous injection of technetium-99m, the pattern of radioactive blood flowing through the heart and great vessels is continuously pictured and recorded on a video storage system for analysis. As discussed by Karliner and Sobel, this method is useful in determination of ventricular volumes, ejection fraction, and abnormal regional contraction in patients with acute and chronic coronary artery disease. Another radioisotope technique is that of myocardial imaging obtained several minutes after intravenous administration of radioactive substances, such as cesium and potassium, which quickly concentrate in normal heart muscle and remain there for a few hours. Ashburn showed that, as the result of non-pickup of these radionuclides by infarcted myocardium, necrotic areas are detected as filling-defects on the cardiac scintillation picture. Further, since ^{43}K is not concentrated in areas of ischemic heart muscle, these regions can be detected by comparing cardiac images obtained with this isotope before and following treadmill exercise. In the future it may be possible to contrast viable muscle with infarcted tissue, since certain radionuclides such as gallium and technetium-labeled tetracycline appear to be preferentially concentrated in infarcted myocardium.

It is clear that recent advances in non-invasive techniques have already contributed greatly to clinical cardiology and there is considerable promise of extension of these exciting developments in the future. Certain of the new non-invasive methods even appear to be capable of providing more accurate information than invasive examination, such as some of the measurements obtained by echocardiography, while other non-invasive techniques serve as valuable screening tests for the identification of patients who should undergo more precise assessment by cardiac catheterization.

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Can Standardized Medical Care Really Be Humane?

AS A NATION we have just embarked upon a massive Congressionally mandated effort to develop and apply professional standards for medical care. Also as a nation we have embarked on a massive effort to assure that medical care will be dignified and humane for everyone regardless of social, economic or political circumstance.

The professional standards now being considered under the Congressional mandate are somewhat at variance with traditional professional standards in medical care. There is reason to believe that they are to be more a convenience to the government for purposes of insurance payment control, rather than for any particular benefit for the consumer or patient. Traditional professional standards, on the other hand, have addressed themselves to assuring appropriate care of high quality administered with human concern to meet the needs of an individual patient. The emphasis was always on what was good for the patient. It is noteworthy and now to be emphasized that the concept of professional standards has been given an additional meaning and an additional purpose. The new meaning and the new purpose will bring about some kind of standardization of medical care which no doubt will have to meet at least some of the requirements of the federal bureaucracy and its computers; and the question is whether this standardized medical care can or will really be humane—that is, responsive to human needs and personal dignity. Medical care must be of high quality and it must also be flexible if it is to meet the human needs. In a very real sense it abhors standardization, just as bureaucracies and computers abhor flexibility.

Under Public Law 92-603 the medical profession is being given a chance (until 1975) to show whether or not it can bring its traditional professional standards for good patient care, which are oriented toward the application of medical science and technology to meet patient needs on an individual basis, somehow into satisfactory relationship with the kind of standards which the government requires to authorize payment of public funds and to curb excessive expenditure of these funds. In this situation where there are two conflicting aims to be rationalized, government must and will press for some kind of acceptable standards and medicine should press for appropriate recognition of human values and for the humane aspects of medical care for any and all persons. Government should respect this primary concern of medicine, and medicine should respect the need of government for some reasonable standards of quality and service for its administrative guidance in paying for care from the taxpayer's pocket.

The question whether standardized medical care can really be humane therefore remains to be answered. In the development and application of the new mandated standards, it is up to physicians to espouse the cause of dignified, compassionate and personalized care which will be flexible enough to meet human needs as well as sound in scientific and clinical criteria. Success will not come easily. It will take a bit of doing, and only practicing physicians and the organized profession can do it. This is a clear duty in the interest of our patients, our patients to be, and the public.

—MSMW

CORRECTION

In the article "Pyogenic Vertebral Osteomyelitis in Heroin Addicts," which appeared in the July issue of California Medicine, a mistake in editing reversed the distinction between Gram-negative and Gram-positive organisms.

The error, on page 4, is in the paragraph beginning "Because of the wide variety . . . "

The second and third sentences in the paragraph should have read: In osteomyelitis due to Gram-positive bacteria, a bactericidal antimicrobial agent should be used whenever possible. The Gram-negative organisms encountered in these infections are frequently resistant to many antimicrobial agents, including the few clinically useful bactericidal agents.

CASE REPORTS

Refer to: Cone LA, Fensterer FS: Tetanus following a dental operation. Calif Med 119:57-58, Sep 1973

Tetanus Following A Dental Operation

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About 60 percent of all patients with tetanus experience injuries to their extremities before the onset of the disease.[1] Although most are due to farm or garden-related wounds or lacerations,[2] "urban" tetanus more often results from the use of contaminated syringes or needles in heroin addicts.[3] Occasionally tetanus follows surgical or obstetrical[4,5] procedures and in rare instances complicates dental surgical operations.[1,5,6] In about 7 percent of the proven cases of tetanus, no obvious portal of entry can be determined.[1] The following report suggests that the patient acquired tetanus during a dental surgical procedure.

Report of a Case

A 59-year-old Caucasian woman was transferred to Lenox Hill Hospital in New York City from another institution for further evaluation and treatment. She had been in excellent health. Then, three weeks before admission, a peridontal abscess that was discovered at a routine dental examination was treated with curettage, scaling and antibiotics. The patient then was well until, a week before admission, she began to have pain in the throat. She was treated by her private physician with 250 mg of penicillin by mouth three times a day for five days. Several days later, mild trismus was noted and the patient was admitted to a hospital, where results of laboratory studies, including a spinal fluid analysis, were within normal limits.

Difficulty in breathing developed and the patient became hypoxemic and stuporous. Tracheostomy was performed on the third hospital day and she then became alert and was able to communicate by writing. Spasticity of the extremities developed, however, and she was therefore transferred to Lenox Hill Hospital for further evaluation and treatment. The patient said she had had no recent puncture wounds or injections other than dental, and had taken no medications other than the penicillin already mentioned. She had been receiving dexamethasone (Decadron®) intravenously while at the other institution. Past history, review of systems, social history and family history were unremarkable.

At the time of physical examination upon admission the tracheostomy tube was in place and the patient appeared to be in no acute distress. The temperature was 37°C (98.6°F), the pulse 104 and regular, respirations 24 and blood pressure 130/80 mm of mercury. Significant physical findings were limited to the neurological examination. The patient was irritable and had pronounced trismus. She was able to communicate by gesticulation and could move her eyes in all directions. Her legs were held in rigid extension with both feet in plantar flexion. She was able to breathe spontaneously through the tracheostomy tube. Sensory functions were apparently within normal limits, but examination was limited because of the patient's irritability. The deep tendon reflexes were 3 plus bilaterally in all extremities, and questionably positive Babinski's reflexes were noted.

Admitting laboratory data, including results of a lumbar puncture, were essentially within normal limits except for a creatine phosphokinase of 1,450 units. An x-ray film of the chest showed no pathologic change, and an electrocardiogram revealed

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Submitted, revised, May 11, 1973.

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a sinus tachycardia with a ventricular rate of 105 and non-specific ST-T wave changes.

The patient was given 3,000 units of tetanus immune globulin, aqueous penicillin G, 2 million units every four hours, sedation and anti-spasmodic and supportive treatment. A dental consultant noted a sinus tract 7 mm deep in the maxilla, in the area of the root of a missing maxillary right molar tooth. Culture of material from this area grew out Pseudomonas aeruginosa and Klebsiella sp. Anaerobic cultures were sterile on several occasions.

A protracted hospital course was complicated by paroxysms of hypertension, cardiac arrhythmia, gastrointestinal bleeding, respiratory tract infection and prolonged sedation following the use of tranquilizers. She nevertheless made an excellent recovery and was discharged after 53 days. Propranolol (Inderal®) appeared to be partially effective in controlling the episodes of paroxysmal hypertension and tachycardia.

Comment

Although the incidence of tetanus in the United States is decreasing, nearly 200 cases[7] are reported annually to the Center for Disease Control. It is particularly in urban areas, where farming and gardening injuries are not likely to be a source of infection, that one must suspect an iatrogenesic etiology or illegal drug use. Since this patient denied any injury in several months before the onset of illness and received no medical therapy other than the dental operation, it seems logical to assume that the latter was related to the development of the disease. The prolonged prodrome of dyphagia likewise suggests that the mouth may have been the portal of entry. Clostridium tetani could have been present in the mouth at the time of operation. In addition, the presence of a dental abscess itself may have provided the nidus for the tetanus bacillus. On careful evaluation of the autoclaving procedure, no fault could be found with the sterilization of instruments. The failure to isolate C. tetani from the mouth a week after the onset of the disease and nearly three weeks after the operation cannot be considered as gainsaying the oral portal of entry, since organisms are cultured from only a third of the infected wounds in proven cases of tetanus.[8]

Of the three previous references to tetanus complicating oral surgical procedures[1,5,6] only that of Zylka[6] describes a case in detail; and it also mentions other cases by Kneise and a statement in a German text that odontogenous causes of tetanus are known to occur. In Zylka's case the patient was a four-year-old girl in whom signs of tetanus developed three days after incision and drainage of a periodontal abscess. Clostridium tetani was not isolated from material that drained from the lesion.

Consistent with previous observations that 95 percent of patients with tetanus have never had an injection of tetanus toxoid, the subject of this case report had never been immunized. This further supports the recommendation that the tetanus-immune status of pregnant women, the elderly and patients undergoing surgical procedures be appraised before operation.[9,10]

Finally, there was in this patient an indication that the difficult problems of paroxysmal hypertension and tachyarrhythmia which often occur during the second week of tetanus may respond to small doses of parenterally administered propranolol.

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Refer to: Ching AD, Wolf SM, Ruskin J: Cryptococcosis—A cause of calcified intracranial mass lesions. Calif Med 119:59-64, Sep 1973

Cryptococcosis

A Cause of Calcified Intracranial Mass Lesions

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CRYPTOCOCCUS NEOFORMANS is the most common fungal infection of the central nervous system. Clinical manifestations of this infection are protean and may simulate primary psychiatric illness, tuberculous meningitis, sarcoidosis of the central nervous system or brain tumor. Chronic meningitis is the usual manifestation of central nervous system cryptococcosis. Occasionally granulomata may occur which are large enough to act as intracranial mass lesions. We had the opportunity to observe a patient with multiple intracerebral cryptococcomas in whom negative india ink preparations and fungal cultures of spinal fluid obscured the cause of illness. Other striking features of his cryptococcal infection were the development of intracerebral calcifications and positive radioisotope brain scans.

Report of a Case

In July 1970 a 47-year-old white man was admitted to hospital in Honolulu, with complaint of urinary incontinence and weakness of the left arm and leg. During the preceding 16 months he had received psychiatric treatment for alcoholism and depression. He had a history of rheumatic heart disease without symptoms of cardiac decompensation.

On physical examination he had murmurs of aortic stenosis and insufficiency, hepatomegaly, psoriasis, and mild left hemiparesis. An x-ray film of the chest showed a 2.5 centimeter coin lesion in the left mid-lung field which had not been present on a film taken in January 1969; this was presumed to be a pulmonary infarct. Skull films were normal. Cerebrospinal fluid examination (Table 1) showed increased protein, normal sugar, and slight pleocytosis. Routine culture and an india ink stain of the fluid were negative. A brain scan showed multiple areas of increased isotope uptake.

The patient improved on supportive care and antibiotics and was discharged in August 1970 with diagnoses of chronic alcoholic encephalopathy, multiple cerebral infarcts (although cerebral carcinomatosis was also considered), left lung infarct and rheumatic heart disease with aortic stenosis and aortic insufficiency.

Subsequently, he had two episodes of weakness

TABLE I—*Results of Examination of Spinal Fluid*

Date	*Opening Pressure mm/Water*	*White Cell Count/mm³*	*Mono-nuclear*	*Protein Mg%*	*Glucose Mg%*	*Routine Culture*	*India Ink*	*Fungal Culture*	*AFB Culture*
8/10/70	150	7	5	116	61	—	—	..	..
12/ 9/70	320	41	36	93	63	Erwinia	—	—	—
12/14/70	..	50	48	..	..	—	..	—	—
2/ 5/71	225	14	12	77	50	—	..	..	..
7/ 8/71 (PEG)	..	5	2	48	50	..	..	..	..
7/19/71 (Ventricular)	..	4	4	19	75	..	..	..	..
8/ 4/71	320	62	59	60	48	—	..	..	..
8/21/71	320	197	167	82	20	—	—	—	—
8/27/71	190	8	6	114	65	..	—	..	—
9/24/71	395	30	28	45	33	—	..	—	—
10/ 8/71	360	37	11	115	45	..	..	..	..
10/15/71	400	580	116	90	40	—	..	—	..
10/22/71 (Ventricular)	..	1	0	16	72	—	..	..	..
11/11/71	240	41	41	60	48	—	..	..	..

—=Negative

From the Southern California Permanente Medical Group, Los Angeles (Drs. Ching, Wolf and Ruskin); the Department of Neurology, University of Southern California School of Medicine (Dr. Wolf); and the Department of Medicine, University of California, Los Angeles, School of Medicine (Dr. Ruskin).

Submitted November 7, 1972.

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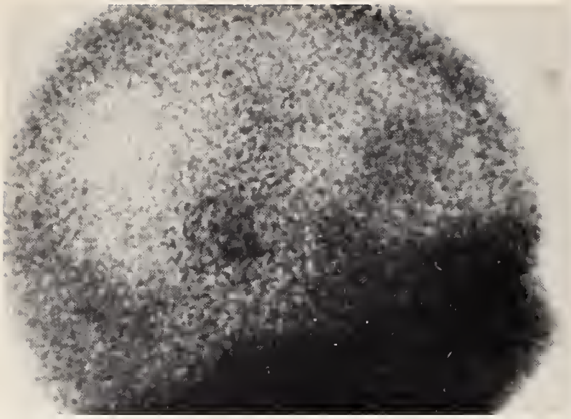

Figure 1.—Brain scan, showing multiple abnormal foci of increased isotope uptake.

and clonic movements of the right upper extremity. A brain scan in October 1970 again showed multiple abnormal foci. The patient was readmitted to hospital in November 1970. Examination revealed impaired mentation, increased deep tendon reflexes in the left extremities and ataxic movements of the left leg. Cerebrospinal fluid (Table 1) showed moderate mononuclear pleocytosis, increased protein and normal glucose. In addition, a Gram-negative rod was cultured from the fluid; it was later identified as an Erwinia species.

The patient was thought to have either vasculitis or multiple septic emboli from rheumatic valvulitis. Multiple blood cultures were negative. Administration of tetracycline, prednisone, isoniazid and diphenylhydantoin was begun. On this regimen his mental condition gradually improved and he was discharged in January 1971. At this time the patient and his family moved from Hawaii to California. He continued to take prednisone, 20 mg a day, isoniazid, and penicillin V.

On 6 June 1971 the patient had a major motor seizure and was admitted to Kaiser Hospital. Babinski's sign on the left was noted postictally, but results of neurological examination the following day were within normal limits. An electroencephalogram showed a focus of 2 to 4 cycles per second slow activity in the right temporal region with a smaller amount of slowing in the left temporal area. A technetium^{99} brain scan demonstrated increased uptake in the right posterior temporal, left parietal and right frontal areas (Figure 1). Skull films (Figure 2) now showed multiple intracranial calcifications of varying size ranging from 0.5 to 0.75 cm in diameter.

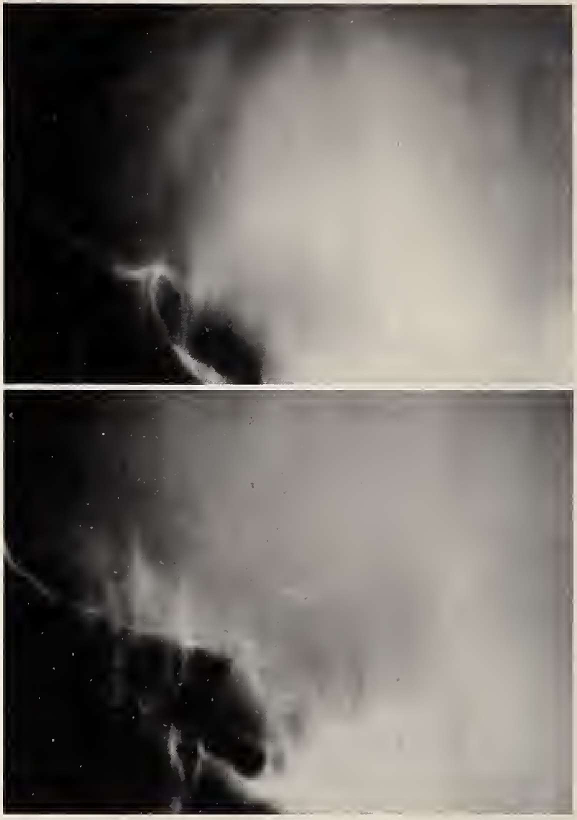

Figure 2.—Laminograms of skull showing intracerebral calcifications in the left parietal region and in the right temporal area just superior to the right anterior clinoid process of the sella turcica.

Bilateral carotid angiograms showed stretching of the thalamo striate veins bilaterally, suggesting moderate enlargement of the lateral ventricles. Pneumonencephalography showed normal subarachnoid cisterns and cerebral sulci, but the ventricular system could not be filled. A ventriculogram on 19 July 1971 showed dilated lateral ventricles without evidence of ventricular obstruction. However, indentations into the ventricular system suggested multiple small mass lesions.

In late August 1971, the patient complained of severe headaches. Examination showed mild nuchal rigidity, confusion, nystagmus on lateral gaze to either side, Babinski's sign on the left and ataxic movements of the left arm and leg. On lumbar puncture (Table 1) the fluid showed a pronounced increase in the number of white cells and for the first time an abnormally low glucose value. The prednisone dosage was tapered beginning on 26 August 1971 and was finally discontinued 5 September 1971. Previous attempts to reduce corticosteroid therapy had always resulted in mental deterioration.

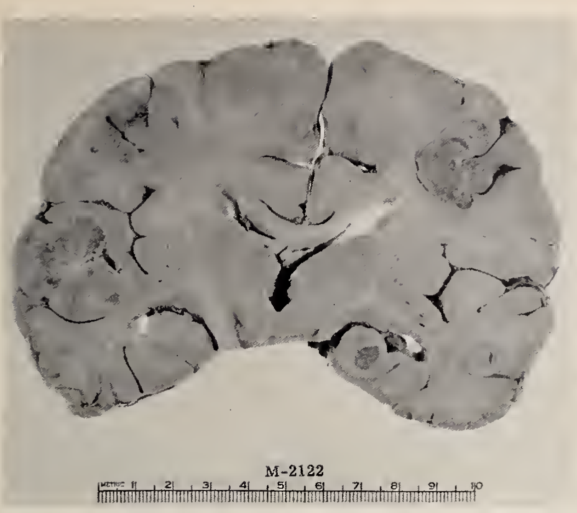

Figure 3.—Coronal section at the level of the red nucleus showing multiple granulomas. Small granulomatous lesions are seen in the right parasagittal region and in the right substantia nigra.

At diagnostic craniotomy performed 2 September 1971, a yellow, firm 2×1.5 cm mass was removed from the medial tip of the right frontal lobe. India ink mounts and permanent sections from this tissue revealed multiple encapsulated yeasts, typical of Cryptococcus neoformans. Culture of the excised tissue was subsequently positive for the fungus. Intravenous administration of amphotericin B was begun. On 10 September 1971, results of cryptococcal antigen titers by latex agglutination were reported to be 1:8 in spinal fluid and 1:4 in serum.* Cryptococcal antibody titers were negative.

On 20 September 1971, after a cumulative intravenous dose of 690 mg of amphotericin B, the patient began to have grand mal seizures. Babinski's on both sides, increasing confusion and ataxia were noted. Ventriculograms showed a mass in the inferior portion of the left cerebellar hemisphere. A second craniotomy was performed and a 2.5×1.5 cm cryptococcal granuloma was excised from the left cerebellum. Cerebrospinal fluid cryptococcal antigen titer was 1:2 on 4 November 1971, by which time the patient had received 1,730 mg of amphotericin B intravenously. He died suddenly on 24 November 1971.

Autopsy

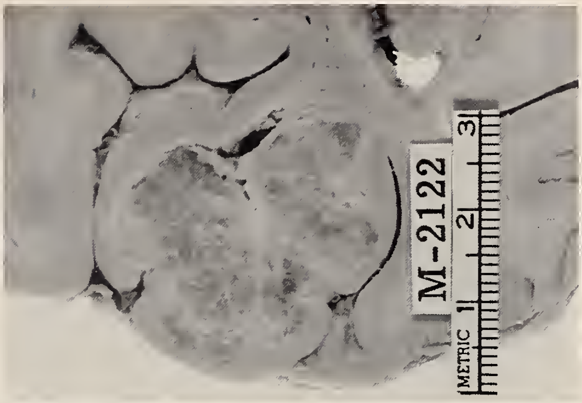

Figure 4.—Detail of granuloma, showing sharp circumscription, grossly visible septations and gelatinous appearance of intervening areas.

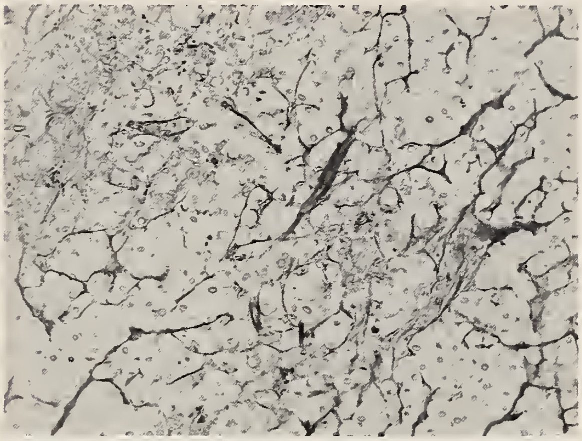

Figure 5.—Section of one granuloma, showing fibrous connective tissue septae and numerous organisms.

The brain showed multiple firm tan lesions varying from 0.3 to 3.5 cm in diameter (Figures 3 and 4). These lesions, some of which were grossly gelatinous, were found in the cerebral hemispheres, cerebellum and pons. Microscopically they were identified as granulomata with minimal to moderate amounts of fibrous connective tissue within the walls and with abundant chronic inflammatory response. Giant cells were seen only rarely. Within the granulomas were innumerable cryptococcus organisms (Figure 5). In the adjacent brain tissue there was mild to moderate gliosis and demyelination. There were several other torulomas in the meninges surrounding the pituitary gland. No evidence of cryptococcal infection was found in other organs. Severe fibrous thickening with dystrophic calcification of the aortic valve, consistent with healed rheumatic valvulitis was observed. There was no evidence of bacterial vegetations. The lungs were unremarkable except for the changes of apical pulmonary emphysema. The liver was enlarged and microscopic examination showed moderately extensive portal cirrhosis.

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*Performed at the Center for Disease Control, Atlanta, Georgia.

Discussion

Cryptococcosis almost always presents clinically as meningitis. However, unusual forms of this disease with granulomas of the brain or spinal cord are occasionally seen.[1] Vijayan et al[2] discovered only 23 confirmed cases in a review of the literature and personally studied one more. Three of the 24 patients were totally asymptomatic during life. In the symptomatic cases the usual clinical presentation was that of an intracranial mass lesion with symptoms and signs determined by the size and location of the tumor. Symptoms preceded hospital admission by from two weeks to 12 years. In 15 of the 20 symptomatic cases the lesion was single and isolated. The cerebrospinal fluid was entirely normal in four cases. Increased protein, lymphocytic pleocytosis and decreased sugar were common abnormalities in the remaining 16 cases.

Reports of calcification within intracranial torulomas are even more rare. Neuhauser and Tucker[3] described multiple, generally punctate areas of calcification on skull x-ray fiims of three infants who at autopsy had multiple cryptococcal granulomas. Three other cases of calcified torulomas are mentioned by Carton and Mount.[1] In a case reported by Liu,[4] five separate "balls" of calcification about 1.2 cm in diameter were identified on skull films; at operation five calcified cryptococcal granulomas were removed. One other instance in a man with undiagnosed meningitis was briefly mentioned during a clinicopathological conference.[5] At autopsy a toruloma near the sella turcica had healed with calcification and then had broken down to cause recurrent meningitis and death. Only one patient besides the one herein described has been reported as having a positive brain scan associated with a cryptococcal granuloma.[6]

Microbiologic diagnosis of cryptococcal meningo-encephalitis rests on culture of Cryptococcus neoformans from cerebrospinal fluid or direct visualization of its budding encapsulated yeast forms in the fluid by staining with india ink. Unfortunately, in recent years there have been numerous case reports documenting cryptococcosis of the central nervous system in which india ink preparations are negative (or misinterpreted)[7] and lumbar sac cultures are sterile.[8-10] This is amply demonstrated in the present case, in which on several occasions india ink smears and cultures on fungus media of large amounts (20 ml) of spinal fluid concentrated by Millipore® filtration failed to grow the organism.

It has been suggested that if cryptococcal disease of the central nervous system is suspected, isolation of the fungus from sites outside the central nervous system may provide indirect evidence of associated neural involvement. Such sites include urine and lung.[11] Since the respiratory tract is the presumed portal of entry for the organism, unexplained lung nodules or diffuse infiltrates in appropriate patients should be examined for cryptococci. In this regard, transbronchial brush biopsy, a minimally invasive procedure, was recently used successfully for rapid identification of viable cryptococci in a pulmonary nodule.[12] Isolation of cryptococcus from sputum alone may have less diagnostic significance since saprophytic colonization by the fungus without overt pulmonary disease has been demonstrated.[13,14] Of interest is that the patient in the present case was noted to have a pulmonary coin lesion during his time in hospital in Hawaii. Unfortunately, the cause of this lesion was never clarified; it most likely represented the primary focus of cryptococcal infection.

Efforts have been made in the last several years to develop serologic test methods for cryptococcosis which would circumvent problems associated with detection and cultural isolation of the organism. Initial attempts were thwarted, however, by inconsistent demonstration of antibodies in patients with frank clinical disease. Recent investigation has concentrated instead on recognition of circulating cryptococcal polysaccharide antigen.[15-17] In fact, presence of this antigen in serum and especially in spinal fluid has correlated best with active fungal infection. Failure to demonstrate diagnostic titers of antibody from similar specimens of body fluid is presumed to be due to neutralization (or complexing) of antibody by excess antigen.

Goodman et al[9] reported three cases of india ink-negative and culture-negative chronic meningitis secondary to cryptococcus which were diagnosable solely on the basis of positive cerebrospinal fluid latex agglutination tests for cryptococcal antigen. The initial diagnostic brain biopsy in the present case preceded, by eight days, receipt of the report that his cerebrospinal fluid and serum contained cryptococcal antigen; in retrospect, specific antifungal drug therapy might have been initiated without resorting to diagnostic craniotomy in view of this positive serologic test. Furthermore, in a number of cases efficacy of antifungal chemotherapy has coincided with reduction of excess cryptococcal antigen levels.[9,18] In the present case the cerebrospinal fluid antigen titer fell from 1:8 to 1:2 after 1,730 mg of amphotericin B. Antibody determinations by tube agglutination and indirect fluorescence were negative on both occasions.

No serologic test provides 100 percent diagnostic reliability and false-negative tests for cryptococcal antigen have been reported in culture-positive cryptococcosis.[15-17] Roberts et al described a patient with intracerebral cryptococcal granulomas in whom no antigen was demonstrable in cerebrospinal fluid or serum.[6] Serologic determinations were made, however, after therapy and the authors suggested that a negative test could have reflected eradication of infection. It is still reasonable to expect that when cryptococcal infection occurs as circumscribed intracerebral mass lesions, immunologic detection of antigen in remote sites (namely, lumbar sac cerebrospinal fluid or serum) would be significantly more productive than attempts to visualize or isolate fungus from similar sites.

Treatment of invasive cryptococcosis remains less than optimal. Although effectiveness of amphotericin B in reducing fatality in cryptococcal meningitis is not disputed, relapse requiring supplementary treatment courses with this toxic drug and neurologic residua are not uncommon.[8,11] Moreover, after many years of experience with amphotericin B a "curative" total dose has not been established. Recommended total dosage ranges between 2 and 2.5 grams intravenously in adults,[8] or about 35 mg per kilogram of body weight. Various modes of administration have been used in attempts to avert drug toxicity. One approach has been to administer generally lower doses (15 to 40 mg) of amphotericin B daily such that peak serum levels are at least twice those necessary for *in vitro* inhibition of fungal growth;[19] another approach is to give higher doses (1 to 1.5 mg per kg of body weight) of amphotericin B on an every other day schedule.[20] Nevertheless, some degree of nephrotoxity is an almost invariable accompaniment of dosage in this latter range.

None of these intravenous regimens, however, has attacked the problem of poor penetrance of amphotericin B into the central nervous system. This problem of drug diffusion was particularly critical in the present case because of gross cryptococcal abscess formation and resultant internal hydrocephalus. Despite the exquisite sensitivity of his cryptococcal isolate to amphotericin B (minimum inhibitory concentration = 0.06 mcg per ml*), it was not unexpected that viable cryptococci were readily cultured from his surgically removed lesions while he was receiving large doses of the drug intravenously. Although amphotericin B has been given intrathecally (either in the lumbar sac or intraventricularly via an Ommaya subcutaneous reservoir[21]), there is insufficient clinical experience to evaluate its efficacy in the treatment of intracerebral torulomas.

A new orally administered anti-fungal compound, 5-fluorocytosine, may prove to be a rational alternative to amphotericin B in treatment of cryptococcal meningitis.[6,22-24] Readily achievable levels of this drug in cerebrospinal fluid are much in excess of the minimum inhibitory concentration of most strains of Cryptococcus neoformans. An investigational supply of 5-fluorocytosine arrived at our hospital the day our patient died. Unfortunately the organism in this case was not especially susceptible to the drug (minimum inhibitory concentration = 6 mcg per ml with a minimum fungicidal concentration = 200 mcg per ml*). Since cryptococci exhibiting high level resistance (that is, greater than 1,000 mcg per ml) may emerge during therapy with 5-fluorocytosine,[24] it may not be prudent to employ the drug alone unless clearly fungicidal levels in cerebrospinal fluid can be achieved. In view of the relative *in vitro* resistance of our patient's cryptococcal isolate to 5-fluorocytosine, fungicidal concentrations of the drug in his spinal fluid would not have been attainable. There is, however, mounting evidence that combining 5-fluorocytosine with amphotericin B may be a more efficacious approach to anti-fungal chemotherapy.[23] Synergistic activity of this drug combination has been demonstrated *in vitro* against a variety of yeast-like organisms including cryptococcus,[25] and emergence of 5-fluorocytosine-resistant organisms in experimental murine cryptococcal meningitis has been reduced by simultaneous administration of the two drugs.[26] Neverthelesss, controlled clinical trials utilizing such drug combinations in human disseminated cryptococcosis remain to be performed.

It is of interest to speculate whether any significance can be attached to isolation of Erwinia species from this patient's spinal fluid. Although there have been some recent reports of septicemic and central nervous system infection in man caused by Erwinia species,[27,28] many of the bacteremic episodes occurred in hospitals where intravenous infusion sets contaminated with the organism were used.[29,30] Indeed, the Erwinia species was isolated from our patient during the peak of this epidemic of nosocomial bacteremias.

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*Kindly performed in the laboratory of Dr. A. I. Braude, UC San Diego, utilizing a method described by Shadomy (Appl. Microb 17:871-877, 1969).

Summary

A case of multiple cryptococcal granulomas of the brain in a 47-year-old white man is described. The initial presentation was that of psychiatric illness. Unusual features of this illness were the presence of multiple intracranial calcifications as observed on skull x-ray films and foci of increased isotope uptake on brain scan. Multiple india ink preparations and fungus cultures of cerebrospinal fluid were negative. Diagnosis of cryptococcosis was not made until brain biopsy. The importance of serologic testing of both blood and spinal fluid for cryptococcal infection in patients with undiagnosed chronic meningitis or atypical cerebral space-occupying lesions is stressed.

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LETTERS *to the Editor*

More on Botulism

To the Editor: The article on botulism in the May 1973 issue of your journal is timely.[1] The recall of three contaminated commercial mushroom products[2-4] and the occurrence of an outbreak of botulism attributed to commercial peppers[5] within the last six months again illustrate the potential dangers of inadequately processed commercial foods. In general, we agree with the discussion and recommendations made by Drs. Werner and Chin, but feel that certain points are worthy of additional clarification and comment.

The authors indicate that "only rarely do patients with botulism have gastrointestinal symptoms." In a recent review of our experience, gastrointestional complaints were present in over 50 percent of outbreaks of botulism reported to the Center for Disease Control (CDC) between 1953 and 1969.[6] In the recent type B outbreak caused by the commercial peppers[5] all eight patients experienced abdominal cramps and vomiting early in their illness. It is thus apparent from our experience that gastrointestinal symptoms should not be considered rare in the symptom complex of botulism.

Though Clostridium botulinum has rarely been isolated from the feces of patients with botulism, we believe this is partly a consequence of physicians' and laboratories' not obtaining stool specimens for examination. We suggest that stool specimens be routinely obtained and examined both for C. botulinum and for botulinal toxins. In the recently investigated type B outbreak, we documented for the first time in this country the presence of botulinal toxin in the stool of three persons, confirming previous Japanese reports.[7,8] None of the patients we studied had detectable levels of toxin in their blood, but type B botulinal toxin was found in the incriminated peppers.

The usefulness of the electromyogram in confirming suspect cases of botulism is worthy of mention. Although the electromyographic patterns exhibited by patients with botulism are not specific, in our experience the electromyogram has been helpful in differentiating botulism from other neurologic diseases. Facilitation of muscle action potentials on repetitive nerve stimulation, in particular, correlates well with the diagnosis proven by other laboratory tests.[9]

In addition to the suggestions of Drs. Werner and Chin about the public health management of botulism we would also include the need for immediate notification of public health authorities, including the local or county and state health departments and federal agencies such as the Food and Drug Administration and CDC. Prompt reporting of foodborne diseases from different locations has in the past brought to light serious interstate problems involving commercial foods.[10]

We agree with the authors that persons who may have been exposed to botulinal toxin by consuming food from an incriminated production lot should receive antitoxin at the first indication of possible symptoms of botulism and stress that gastrointestinal symptoms may commonly be the first manifestation. However, we feel that antitoxin should also be administered to all individuals who have consumed the specific food responsible for an outbreak of botulism and are seen within seven days of exposure, even in the absence of abnormal signs or symptoms.

Drs. Werner and Chin state that botulinal antitoxin does not reverse paralysis that is already present. However, there is some evidence to the contrary; in particular, some patients with type E botulism have shown dramatic improvement within hours after receiving antitoxin.[11,12]

Good respiratory care is of critical importance in the successful therapeutic management of botulism. We agree that prophylactic tracheostomy is not mandatory and that respiratory paralysis may be present for a brief period. However, we question the wisdom of employing an endotracheal tube for periods as long as a week as the authors have recommended.

Dr. K. F. Meyer, who has contributed enormously to the control of this disease, described in the editorial[13] accompanying Dr. Werner's and Dr. Chin's paper the great strides that have been made by the American canning industry in reducing the risk of botulism in this country. New regulations proposed by the National Canners Association, which are now being considered by the Food and Drug Administration, will further minimize if not eliminate the risk of botulism from commercially canned foods. Nevertheless, the ultimate "fall of botulism" may be in the distant future, as it depends on education of the home canner, a continuing public health challenge.

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Sickle Cell Trait Hematuria

TO THE EDITOR: Allow me to make some comments regarding a case report of a patient with sickle cell trait hematuria in the June 1973 issue of CALIFORNIA MEDICINE, presented by Doctors Hoffman and Zucker. They described the use of epinephrine during selective renal angiography in order to diminish the patient's hematuria. In reading the case history, it is apparent that the patient received at least two units of blood and apparently significant intravenous hydration during the patient's illness.

In view of the fact that "modified exchange transfusion and hydration" is the recognized standard treatment of sickle cell trait hematuria at this time, it is puzzling to me how the authors can definitely say that the injection of the epinephrine into the involved kidney was the real reason for the diminution of the bleeding. The patient presented was similar to one I recently treated at Kaiser Foundation Hospital, with simply modified exchange transfusion and hydration. Several days after the last unit of blood was administered, the hematuria cleared completely and has not recurred three months hence.

It should be remembered that nephrectomy for hematuria of sickle cell trait is practically never indicated, and certainly should be resorted to, only in the last resort, since it is not an infrequent occurrence for the patient to bleed first from one kidney, and then at some later date from the other kidney. One thing that is certainly worse than a young patient with sickle cell trait hematuria is a young patient with sickle cell trait who has no kidneys.

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The Authors' Reply

TO THE EDITOR: In response to Dr. Campbell's comments in which he ascribed the cessation in bleeding in our patient to transfusion and hydration, there are several points on which we would take issue.

1. Our patient received a total of two units of whole blood separated by 24 hours. This would hardly represent a modified exchange transfusion in which fresh blood or packed cells in quantities far exceeding two units is administered over a two- to four-hour period.

2. Dr. Campbell remarks that our patient received "apparently significant intravenous hydration during the patient's illness." This must be pure speculation on his part since intravenous or even oral hydration was not mentioned in our case report.

3. To state that "modified exchange transfusion and hydration is the recognized standard treatment of sickle cell trait hematuria" is surely an overstatement. It is recognized that spontaneous remission of hematuria is a frequent occurrence. Treatment with distilled water hydration and urinary alkalinization has been promoted recently.[1] The use of epsilon aminocaproic acid (a urokinase inhibitor) has also been introduced as a possible mode of therapy.[2] Exchange transfusion has been used in pregnant women with sickle cell disease.[3] Obviously no one treatment is the accepted treatment for hematuria in sickle cell disease or trait. We have merely introduced another possible treatment.

We fully realize that the cessation of the hematuria in our patient could have been spontaneous and fortuitous as it could be in those cases where other modes of therapy have been attributed the success. The only method in which one could be sure as to the efficacy of our technique would be to demonstrate the bleeding point angiographically, infuse the kidney with epinephrine, and then reinject with contrast media to determine if the bleeding point had ceased. As stated in our article, the hazard of reangiography is that this may exacerbate the bleeding since the contrast media is a vasodilator. However, perhaps this is warranted to absolutely prove or disprove the efficacy of the technique. A second course of epinephrine could be given.

In response to Dr. Campbell's plea to save nephrectomy as a last resort, I believe if he would reread our article carefully he would find that the genesis of this new technique was because we were striving to avoid nephrectomy.

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Pinpointing Preceptorships

TO THE EDITOR: At the University of California, Davis, School of Medicine, the Department of Family Practice offers electives whereby a medical student can work in the office of a physician in private practice. This physician is the medical student's preceptor. In the past, the Department of Family Practice had a listing of available preceptorships in California. Many of these preceptorships were in small towns and/or remote areas of California. Thus the medical student often had no idea where his preceptorship was located. I suggested that the Department of Family Practice obtain a large map of the State of California and place pins on the map wherever a preceptorship was located. Subsequently, medical students have found it much easier to determine exactly where their preceptorship is located.

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Hemolytic Disease Reporting

TO THE EDITOR: In the recent report by Hawes and Mordaunt on two years' experience with Rh hemolytic disease reporting (Calif Med 118:28-32, May 1973) it is regrettable that no reference is made to the extensive studies which led directly to the legislation that made their report possible. These studies were reported in detail in CALIFORNIA MEDICINE (104:81-88, Aug 1966) and represented a tremendous contribution in time and effort by many California physicians, CMA staff and members of the State Department of Public Health. The reduction in deaths due to Rho (D) hemolytic disease of the newborn in California should very likely be attributed as much to these efforts as to the legislation which resulted, on which the Hawes-Mordaunt report is based.

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On Throw-aways and Such

TO THE EDITOR: For some time I have been troubled by the hundreds of pounds of unsolicited samples, advertisements, "throw-away journals" and various "get rich quick schemes" which arrive in my mail each year. I was pleased to find that the AMA is willing to take my name off the master promotional mailing list at my request. I would urge other physicians who are concerned about the loss in tax dollars through subsidized bulk mailing, not to mention the loss of trees to provide paper for unwanted material, to write to Mr. Robert A. Enlow, Circulation and Records Department, American Medical Association, 535 North Dearborn Street, Chicago, Illinois 60610.

JOHN C. BOLTON, MD
San Francisco

Refer to: Root I, Scott W: The clinician and forensic medicine.
Calif Med 119:68-76, Sep 1973

Special Article

The Clinician and Forensic Medicine

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Although it is an intrinsic part of all medical practice forensic medicine often is either unrecognized as such or is consciously or subconsciously evaded. The failure to apply some rather basic and simple forensic principles that only the physician is capable of doing may result in problems to the patient ranging from frustration to near catastrophe. For physicians who are reasonably well equipped to understand the legal system, the successful conclusion of a legal case, including, sometimes, an appearance in court, can be stimulating and interesting.

FORENSIC MEDICINE is an intrinsic part of the practice of medicine for virtually every physician. It is not reserved for the forensic psychiatrist, the orthopedic surgeon and the forensic pathologist.

We define forensic medicine as that aspect of medicine which involves legal problems and may eventually be settled by court proceedings even though only a few actually go to trial. The matter may be criminal (homicide, rape, assault, a battered child) or civil (traffic injuries, industrial accidents).

As forensic pathologists, we have had an opportunity to discuss with peace officers, with lawyers, insurance adjustors and judges, as well as with other physicians, their opinions of the level of concern for the legal problems of their patients that is manifested by the medical community. It is our general impression from these conversations that the level varies from barely adequate to nonexistent.

The physician must become involved, for if he does not, vital medical questions which only he can answer will be slighted and justice suffer. An innocent person may be convicted, a criminal may go free, an unfair settlement involving a large amount of money may be paid in a civil suit or may be unfairly denied to one who deserves it. The consequences to the patient may range from frustration to near catastrophe. Most of the literature related to forensic medicine has appeared in publications not readily available to or read by most physicians, but rather is in the forensic science journals or law journals.

For three years, there has been an active Forensic Medicine Committee of the San Bernardino

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County Medical Society with lawyers, peace officers, coroners and physicians of several disciplines making up the membership. Under this sponsorship, lectures and programs have been presented to hospital staffs and medical meetings in the county. In addition, the authors have lectured to medical students at the University of California at Irvine School of Medicine and have prepared a syllabus on forensic medicine for their use. This article is to a large extent taken from the material prepared for these lectures. It is hoped that it will serve as an introduction to some of the aspects of forensic medicine that may be encountered by any physician and will help make him more comfortable and more useful to his patients in such matters.

It may seem elementary to urge the preparation of a carefully worded and complete medical record, but remember that in most cases, even if they go to trial, a well prepared, clearly understandable medical chart will be stipulated to, and obviate the need for the doctor's appearance in court.

Medical History

The primary source of the medical history is the patient, but other sources should be utilized, including the family, companions or police authorities. The police, in particular, may be a valuable and, occasionally, the only source of information. (They in turn have a need and a right to know about the patient's condition. They should further be permitted to interview the patient as soon as possible consistent with reasonable medical care. Failure of the physician to permit this to the extent that is reasonable may be construed as capricious, deliberate obstruction of justice.)

The approach to the patient is somewhat different than in the routine medical examination. The chief complaint and the history of the present illness or occurrence should be recorded as nearly as is practical and possible in the patient's own words. Specific direct questions may be useful to obtain a detailed picture, but they may cause the patient to be deceptive. For reasons of guilt, complicity, embarrassment or financial gain, it may seem to the patient to be to his advantage to be less than candid, so the physician must have a high index of suspicion. He should be alert to discrepancies in the history as obtained from the patient or other sources as well as conflicts between the history and subsequent physical or laboratory findings. The disparities should be carefully noted in the medical record, but it is not necessary or perhaps even desirable to confront the patient with them, for usually this can serve no purpose in the immediate care and may damage the doctor-patient relationship. Discussion of the discrepancies with the proper authorities may well be in order, however.

Physical Examination

Although we are taught very early that only descriptive terms and not diagnoses should be used to record physical findings, there is all too often a tendency to forget this admonition when describing injuries. Remember the accurate definitions of descriptive terms. A laceration is a ragged, tearing wound while an incision is a cleanly cut wound. A bruise is a discoloration due to extravasated blood under the surface. An abrasion is a scraping away of surface layers. Describe the shape of each injury as accurately as possible, such as linear, curved, broad, narrow, stellate, regular or irregular. The depth of penetration should be noted. Describe the location of each wound in relation to a fixed anatomic landmark. The size should be recorded in units of measure, not by comparison to fruits or nuts—no one knows exactly how big an apple is. The angles and directions of wounds should be given when applicable. All injuries, no matter how minute or how remote from the area of primary interest and seriousness, should be recorded. Any pattern that may be recognized should be described—the grid of a radiator, the imprint of the head of a hammer, an auto emblem, a tire tread. Factors which may assist in estimating the age of wounds, such as color, encrustation, exudate, possible infection, retraction of the skin edges or healing, should be recorded. The presence of any foreign objects or particles in or associated with the wounds should be noted. Photographs may be invaluable in recording physical findings, but they can only supplement, not replace, good descriptions.

Medical Records

The medical records, accurately and legibly recorded, of the history, the physical examination, laboratory or other special studies, progress notes and course of treatment provide the necessary documentation required in later review of the case for either medical or legal purposes. The written record becomes a legally accepted document for any subsequent action.

In an acute, life-threatening situation, there may be numerous chart entries within a relatively short span of time, particularly when several physicians are providing care at the same time. These records may span several pages of looseleaf chart paper. Unless each entry is not only dated, but identified as to time, subsequent review of the course of events may be difficult or impossible.

Gunshot Wounds

Case History. A man was found comatose on his bed at home by his wife. He had been shot. There were no witnesses. No suicide notes were found at the scene. On admission to the emergency room, the physician noted the presence of a wound in the chest and one in the back. His description of these injuries was "entrance wound in the back, exit wound in the chest." This was based on the sizes of the wounds. The chest wound was much larger than the wound in the back. On the basis of this impression, a homicide investigation was begun, since wounds of this nature are not consistent with self-inflicted wounds. The patient died before any definitive therapy could be given, and an autopsy was performed.

The pathologist, after examining the external and internal injuries, was able to state that the wound in the chest was the wound of entrance and furthermore that it was a contact wound that had been enlarged by expanding gases from the muzzle of the gun. The wound in the back was a wound of exit which was small and smooth because the subject was lying on his back on a firm mattress which shored the skin as the bullet exited and minimized the usual stretching and tearing of an exiting bullet. Based upon these findings, the authorities were satisfied that the wound was most probably self-inflicted.

Assume, however, a different outcome. Assume that the subject was taken to surgery for an exploratory procedure. In the course of such exploration, the skin wounds were debrided and no tissue was submitted for pathologic examination. If the subject then died without regaining consciousness and, therefore, could not give a history, the only expert medical opinion available would be that of the admitting room physician: "Entrance wound back, and exit wound chest." In these circumstances, the authorities would have no choice but to conduct a full-scale homicide investigation, and it is entirely possible that an innocent person could be accused or convicted of a crime that did not occur, and even if acquitted could carry the onus of suspicion for life. As illustrated in the case history, the physician's judgment affects not only the patient but may profoundly touch the lives of other people, innocent or guilty.

Once the physician has cared for a gunshot-wound victim, he becomes inexorably involved in the subsequent legal proceedings. The questions which may be asked of the doctor are simple, but the answers may be complex and enormously important. Is the wound an entrance or exit wound? What is the direction and angle of the bullet? What was the distance from the gun to the victim? Could the injury have been self-inflicted? If the original physician is not an expert, he may not know the answers, but if his original description was adequate and careful, an expert may be able to interpret his findings.

The history should be recorded as obtained. The physical examination should include observations of injuries both to the clothing and to the body. The clothing should become part of the physical evidence for detailed examination by ballistics experts. It should be properly identified and carefully handled and preserved. If the clothing must be cut away from the victim, caution must be taken not to cut or tear through the damaged areas which should be left intact. The observations should include:

1. The exact location of the injuries, described by using fixed anatomic landmarks and measurements.
2. The size and shape of the wounds.
3. The nature of the wound—whether round, oval, irregular, smooth or stellate.
4. The nature of the wound edges—whether inverted or everted.
5. The presence or absence of abrasion of the wound edges.
6. The presence and type of any protruding tissue.
7. The presence or absence of burning of the wound edges.
8. Powder tattooing, grease or smoke smudges, their distribution and extent and relationship to the wounds.
9. Powder, grease or smoke smudges on the hands of the victim.
10. Other injuries, such as abrasion, small lacerations or contusions of the hands that could have been caused by the recoil of the weapon.
11. Other recent injuries, however small.

Note: Diagnostic terms—such as entrance or exit wounds, contact, near or far range, low or high velocity missile injury, pistol, rifle or shotgun injury—should be reserved for the diagnosis or impression.

X-ray films should be taken to locate and identify any bullets or fragments which may not have exited from the body. If the bullet is not removed surgically, the x-ray film will give some indication as to the size and type of the bullet, but the estimate may be very deceptive. A bullet of low velocity and small caliber may ricochet within the body so that the location of an entrance wound and the location of the bullet by radiograph cannot in themselves be relied upon as an accurate indication of the course of the bullet in the body.

If the skin wounds are debrided or excised during the course of surgical procedure, the tissue should be submitted to the laboratory carefully segregated in separate containers and labelled as to its source. If the bullet is removed at operation, it should be handled with care, and the use of naked metal forceps upon the bullet should be avoided to keep from destroying markings which may subsequently be used in ballistic identification. The bullet, properly identified, should be submitted to the authorities as part of the physical evidence in the case. If possible, it should be submitted directly by the physician to the police authorities, who should give the physician a written receipt. These procedures will help maintain intact the chain of evidence. Every case involving bullet wounds must be by law reported to the authorities as soon as possible, regardless whether the injury was suicidal, homicidal or accidental.

Injuries produced by guns will be affected by many variables. Hence, there is no absolutely typical picture. Commonly a wound of entrance is round and is smaller than a wound of exit, which may be irregular and stellate in shape. The edges of the wound of entrance may be inverted and abraded. If the wound of entrance is a "contact" wound—that is, with the muzzle of the gun held tightly against the skin but over a directly underlying bone—there may be a gas blast effect, with resultant irregular stellate laceration of the wound. A wound of this kind will be larger than the wound of exit and will not show the typical smooth, rounded, inverted, abraded edges. Also, there may be muzzle abrasion imprints on the skin caused by the explosive gases having forced the skin outward against the gun barrel. If the injury is the result of a near-range firing, there may be deposits of unburned powder or smoke, or tattooing from unburned powder particles. The distribution of this material may aid in determining the range from which the weapon was fired. (The information can be interpreted by authorities in light of the type of powder in the cartridge load.) The extent of smoke-smudging or powder marks should be measured accurately. With distant-range missiles there will be no powder or smoke marks and no gas blast effect. The pattern will be modified if the bullet has ricocheted or passed through another object before entering the body. If it has entered through the clothing, it may carry part of the cloth into the wound. The patterns of shotgun injuries depend a great deal upon the range. It should be borne in mind that penetrating or perforating wounds may be caused by missiles other than bullets and that sometimes these may be confused with bullet wounds.

Stab Wounds

The exact size and location of a stab wound as well as its direction should be accurately noted. Associated bruising is often important to indicate that the haft of the knife struck the skin. The character of the incision—clean, ragged, sharp at each end, dull at one end—may help in defining the weapon. A good description is vital because all these characteristics are lost once the wound is repaired.

It should be apparent that the external appearance of the wound is absolutely no criterion of the depth or direction of penetration or of the severity of internal injuries. Innocuous surface appearances can be deceptive. A small laceration in the upper eyelid may be only the surface manifestation of a screwdriver stab wound that has penetrated through the skull and 5 inches into the brain. Below a small incision in the upper abdomen there may be injuries necessitating laparotomy for treatment and evaluation. In one such case, what was not recognized was that the same wounding blow had also penetrated the diaphragm and lung, with unsuspected hemopneumothorax resulting in the patient's death. Since a knife almost never goes straight in and out, the wound it makes is almost invariably longer than the width of the blade. Elastic fibers of the skin often distort the appearance of a stab wound, and pushing the skin edges back to their original position may help determine the shape of the weapon.

Blunt Injuries

Occasionally the pattern of injuries may help identify what caused it—a bludgeon or other blunt weapon, or some characteristic feature of an automobile. An injury produced by a blow with a piece of 2×4 lumber will have a different appearance if it was struck with the flat surface than if the impact was with the corner of the weapon. Pipe threads may leave a characteristic pattern of fine and closely approximated parallel lines. A beating with a leather belt will leave a different impression than one with an electric cord. Even though the imprint may not be sufficiently characteristic to identify the weapon absolutely, it may permit certain conclusions as to whether a particular type or even a specific instrument could have inflicted the injuries.

Rape

When an accusation of rape is made, it must be remembered that (at least) two persons are involved and that the emotions, the reputations and often the future of both are at stake. It is one of the most vexing of all law enforcement problems for the police, the courts, the physician and, of course, the accused and the accuser. Statements of the parties involved made to officers or the physician are often the only direct evidence relating to consent and ultimately to unlawfulness. The victim is usually terribly disturbed.

All subsequent investigation and court proceedings may only serve to aggravate psychologic trauma. Not infrequently, the woman who has been raped in private will be figuratively raped again in public. She may need a great deal of counseling to get through this very trying, traumatic experience. On the other hand, the accused, if innocent, will suffer a great deal of abuse and embarrassment; and, even if exonerated, may be permanently stigmatized.

A physician cannot make a diagnosis of "rape." That is a legal finding ultimately to be decided by a court of law. Rape is defined as unlawful carnal knowledge of a female without her consent.[1] It should be obvious that the element of unlawfulness is not part of the physician's realm, but he may be helpful, even vital, in the determination of carnal knowledge and sometimes the matter of consent. Carnal knowledge is usually defined as the penetration of the female genitalia to any degree by the penis. Orgasms or seminal emissions are not necessary, and even inability of the aggressor to have penile erection does not preclude the charge of rape. Lack of consent may be supported by medical evidence of the application of force, the administration of drugs or of a specific degree of mental impairment of the victim. Medical evidence may tend to confirm or deny allegations made by the persons involved. But it is possible that rape may be committed without any traces being left on either the aggressor or the victim, and it is also possible that the medical evidence found in alleged rape may have been produced in situations not constituting rape.

In history taking, inquiry should be made into the details of the alleged attack[2]—the span of time, the nature, use and degree of physical force or threat of violence or use of drugs, previous sexual contacts, and whether douching, bathing or medication followed the alleged attack. Also the hour and date the victim is examined, the place of examination and the name of the witness or attendant present, such as the nurse, should be recorded.

The physical examination should take note of the presence or lack of trauma to the face, breasts, genital area and hands and fingernails, or other appearance of areas of trauma. The nature and extent of such trauma should be recorded as well as evidence of how long ago it had occurred. Note should be made as to whether these observations are consistent with the history. Evidence of venereal disease by physical diagnosis or laboratory test should be sought.

In any case involving potential court action, the chain of evidence to be presented is only as strong as its weakest link. One of the weakest potential links is in proper identification and documentation of physical evidence. A smear of vaginal pool material should be examined as soon as possible by the physician or in a laboratory for the presence of sperm, with a note as to the number and motility of sperm if it is present. A smear should be submitted, fixed, to the pathologist for subsequent staining, examination and permanent record. The slide should be marked for identification by the examining physician. Frosted-end slides with the patient's name and other identifying information written on the etched portion with an ordinary pencil will acceptably identify a specimen. Similarly swabbed material should be submitted for acid phosphatase determination. If possible, the slide and swabs should be delivered by hand to the pathologist, and he should make written notes of receipt. If it is not possible to deliver the specimen in person, the exact chain of possession should be recorded.

Additional specimens which are of value to the authorities include any foreign hair adhering to the victim, and it should be separately identified. Any pubic hairs appearing to be semen-encrusted should be similarly handled. At least ten full-length pubic hairs should be cut from the victim (plucked hair is not preferable) and handled in a similar fashion. Any clothing that is damaged or appears to have suspicious stains should be preserved for the authorities.

The Battered Child

The physician is in the enviable position of being able to do something to help the battered child, one whose body has been broken or burned or who is suffering from malnutrition or narcotic addiction. Not only can the physician treat the injuries, he can act to prevent further injuries and possibly death. It is not uncommon in investigating a battered child case to find that the current episode is only the most recent of many.

When an injured child is brought to the attention of a physician, he or a nurse should record at the earliest opportunity all statements made by the adults who accompanied the child relating to the cause of the injury. The physician's observations of the current injury and any other injury or signs of mistreatment in the past should also be noted. One should not forget that the child, not the adult, is the patient, and that if old enough, he should also be questioned separately as to the cause of the injury. Color photographs provide a vivid illustration of the extent of the injuries. Full body x-ray studies are almost mandatory.

When it appears that the injuries may have been deliberately inflicted, it is the duty of the physician to report these observations to the proper authorities. It is up to the authorities, and not to the doctor, to investigate and determine whether or not a crime has been committed, but alertness by the physician may result in the prevention of further injury.

Drugs

The drug victim may be unconscious when first seen in the emergency room of the hospital. He is generally in this condition either as the result of attempted suicide or an overdose of street drugs. Rarely is pure accident the cause. Diagnosis can be made from the history and physical examination. Particular attention should be paid to blood pressure, the respiratory system, the cardiovascular system, neurologic examination and examination of the eye grounds—all these aimed at finding a cause other than chemical for unconsciousness. The skin should be examined for needle tracks, old or recent. The laboratory can help diagnose or rule out hypoglycemia, diabetic acidosis, uremia or anemia as causes of unconsciousness. A test dose of Naline® is helpful in assessing the possibility of opiate poisoning.

If the patient is found to be suffering from sedative overdose, therapy is aimed at supportive measures until he can metabolize or excrete the poison. Except for Naline, no specific antidotes are available and the so-called stimulant drugs probably cause more damage than any possible benefit.

A very important therapeutic measure is gastric lavage. Large amounts of unabsorbed barbiturates or other drugs may remain in the stomach for hours or dozens of hours, so it is never too late to institute lavage and prevent further absorption. In every case, the *first* specimen removed should be saved for laboratory examination. The urine obtained from the catheter should also be saved, as should a specimen of blood. These specimens may later answer many legal questions as well as make your diagnosis and keep you from spending a lot of time hunting rare arthropod-borne encephalitides.

Remember that long-haired, ragged, dirty teenagers can have diabetes and that prosperous, dignified, middle-aged people may abuse drugs or attempt suicide.

The importance of obtaining and saving gastric washings, urine and blood cannot be overstressed.

The Physician and the Court

Lawyers and physicians seem to have antagonism for each other's professions. The sources are not difficult to find, but their relative importance may depend on any one individual's opinion. Physicians often look upon lawyers as prime movers in malpractice suits and as malevolent rascals who try to befuddle and humiliate medical witnesses. Lawyers may regard physicians as evasive and elusive witnesses who will never answer a question directly.

A great many problems can be solved if the two professions understand each other's language. The words "always" and "never" are rarely used in medicine. When a lawyer asks, "Are you sure that the traffic accident caused the patient's symptoms?", the doctor is most apt to refuse to avow that he is "sure" and to start shilly-shallying. When the lawyer persists, the uncomfortable physician feels challenged and may become confused, angry or arrogant. Very often the experienced medical witness can avoid this by answering, "While nothing in medicine is absolutely sure, I can say with reasonable medical certainty, that the traffic accident caused the patient's symptoms."

If the physician recognizes that the lawyer is doing his duty to provide his client with the best representation he can give him and is not personally hostile to the medical witness, a lot of distress can be avoided.

Often questions are asked, especially in cross examination, that are really intended to inform the lawyer or the jury of something, and not to embarrass the witness. The best approach to such questions is to listen attentively and then courteously answer as best one can. If the question is unclear, one should not hesitate to ask for clarification. If the answer the physician wants to give requires explanation to make sense, it is quite in order to ask the judge for permission to explain before answering. Almost always permission will be given. A good rule is: Do not give snap answers, particularly not to complicated questions. If you don't know, say you don't know. Many lawyers after a long succession of questions will attempt to sum up for the witness. The summation is delivered with careful attention to emphasize the points that the lawyer wants emphasized and to play down or ignore the points that he may consider damaging to his case. He then will say, "Isn't that correct, Doctor?" Much of the time, it isn't correct and you should say so. If he has taken remarks out of context, make that plain. If he has glossed over an important point, bring it out. Do not do this, however, simply to demonstrate your own cleverness, but only when you are honestly correcting a false impression that the lawyer may give the court. Very often, long and complicated questions are asked. There is nothing wrong with sitting quietly in the witness chair to consider the question before answering and there is nothing wrong with asking for clarification of the question if you need it. The court reporter can read back the question if that will be helpful.

Surprising or embarrassing questions can often be avoided by pre-trial conferences between the medical witness and one or both attorneys. In a complicated case, if the attorney doesn't ask for a conference, the physician often may wish to do so. Because of the niceties of courtroom procedure, a lawyer may be forced to spend as much as a half-hour attempting to lay a foundation for asking a question which, in a pre-trial conference in the office, he could ask right out, be answered, find out the answer wasn't valuable, and dispense with the whole line of thought.

At a pre-trial conference, a matter which may be settled is the matter of the expert witness' fee. This fee is compensation for the professional time spent in preparing for the trial and in testifying on the witness stand. It is not payment for the testimony rendered. Not often does the question come up in actual court practice but, if it does, remember that you are being paid for your time and not for your answers, and that since time, knowledge and skill are all a physician possesses to provide a living for himself and his family, it is perfectly legitimate to require compensation. In this field more than some others, it is important to bill for your services. You will find that if you do not value your time and knowledge, the lawyers are apt not to value them either. As in other aspects of life, ignorance causes more fear and dislike between the two professions than is ever justified by reality.

Economics and Forensic Medicine

Case History: A 52-year-old man who had been a prison guard in California for most of his adult life had been treated for several years for coronary arteriosclerosis. There were extensive medical records regarding this illness. The man was admitted to a hospital where a diagnosis of carcinoma of the lung was made on the basis of radiographic evidence, supraclavicular lymph node biopsy and cytologic examination of pleural aspirate. He remained in the hospital for three months and died there. His wife refused to sign an autopsy permit and the treating physician signed the death certificate as death due to carcinoma of the lung. Several weeks after the funeral, after the emotional impact of her husband's death had subsided, she realized that as a prison guard her husband had been a law enforcement officer. She recalled that he had been treated for coronary arteriosclerosis, which, in a law enforcement officer is considered to be a work-incurred disability. She applied to the Workmen's Compensation Board for a pension.

Since the death certificate showed the cause of death as carcinoma of the lung, the request was initially denied. When the medical records were reviewed, they were inconclusive as to the extent or severity of coronary arteriosclerosis. Finally, after nine months of legal proceedings, the body was ordered disinterred for autopsy. Although by that time the autopsy findings were partially obscured by postmortem changes, there was clear-cut evidence of an old coronary occlusion. Although the autopsy findings could not shed any light on the terminal illness, a pension was awarded on the grounds of coronary arteriosclerosis. Had autopsy been performed at the time of death, nine months of emotional upset, turmoil and legal cost could have been avoided.

Case History: A man received a compound fracture of the arm in an industrial accident. He also complained of low back pain at the time of the initial examination. Since the back pain did not appear to be of great significance, the physician directed his main attention to the fracture of the arm and neglected to record the symptoms of back pain. Six months later, the fracture was completely healed and asymptomatic, but the patient remained disabled by back pain, which subsequently was shown to be referable to a herniated disc. Since there was no historical record of the back pain at the initial episode, the relationship to this disability and the injuries was of grave doubt in the subsequent legal action.

Of the large number of judicial or quasijudicial actions involving medical facts, the majority are of a civil nature and the final judgment involves a financial settlement. The medical facts may involve either natural disease or accident. The process may be acute, with precipitous onset, or it may have an incubation period of 40 years. The actions may involve private insurance or Workmen's Compensation.[3] They may involve litigation to compensate for damages or injuries due to actual or alleged second party negligence, stress factors or responsibility. In order that the final judgment may not result in denial of just claims or in the award of undeserved compensation, the medical report must be accurate, comprehensive and impartial. This principle applies whether the action involves a living patient or a survivor of a decedent patient.

In the case of acute injuries received in an accident, the possibility of an eventual claim may be apparent from the first physician-patient contact. The physician, however, must be alert to record in the history all of the patient's complaints, not just the most severe or obvious, for these may not be the issue of subsequent action. It is during the initial period, when the patient is in acute discomfort and desperately needs medical care, that the history is most likely to be reliable.

There are situations where the physician may not initially or subsequently recognize the relationship of a disease process or injury to a compensible cause (as in the cases cited above) or in diseases with gradual onset such as silicosis or asbestosis. Does the physician in such instances have a responsibility limited to the immediate care of the patient's complaint, only to leave him or his family to fend for themselves subsequently? Who, then, does the patient turn to? Who else is qualified to provide the needed medical advice and consultation? At what point does our moral obligation as physicians, as human beings, end?

Early in the course of illness or injury, the patient's attitude typically is heavily weighted toward the medical problem—getting well. As the medical problem is resolved, the balance of attention shifts toward the financial considerations. Indeed, this may become the overriding question and significantly affect any subsequent response to therapy. Whether this is conscious or subconscious, the outcome is similar. Prolonged or permanent disability and prolonged expensive, often bitter, litigation may result.

The Coroner-Medical Examiner

The medical legal function of the coroner or medical examiner broadly involves the investigation of death occurring in certain circumstances which, though similar in most jurisdictions, may vary somewhat and are set forth by local or state law. In general, these include deaths that involve actual or possible second party involvement, or deaths that may involve industrial or occupational health or public hazard or health. These functions are most effectively handled through a multidisciplinary approach involving qualified administration, on-the-scene investigation and examination by the forensic pathologist and the toxicologist. At times, other disciplines need to be brought in and some of these may be combined in one person.[4] Given the essential ingredients of competent personnel and community interest and support, the critical variable remains case reporting. Sudden death from accident, suicide or homicide is almost invariably reported to the medical legal office. Many deaths occurring long after an injury are not reported by the attending physician and are not recognized by the registrar of vital statistics as deaths due to injury. If these deaths are related to trauma or industrial or occupational hazard (as in asbestosis or aplastic anemia from chemical exposure) the family may unwittingly be denied financial compensation to which they are entitled. This might be avoided if the death were properly investigated and supporting pathologic evidence obtained from autopsy studies. In addition, the failure to obtain vital statistics related to occupational or industrial hazards and public health and safety vitiates the necessary preventive or corrective measures that should be taken by industry to improve the health of workers.

The role of autopsy in the forensic pathologic investigation of violent death is well recognized and understood. It has not only been discussed extensively in medical literature, but has been widely publicized in lay circles both in nonfiction and in fiction. Less well appreciated but of equal or perhaps of even greater significance to the family or survivors and society, are the economic ramifications of the forensic pathologic autopsy where the question of criminal implication has not been raised. Insurance policies with double indemnity for accidental death or providing death benefits only in accidents are common and may involve large amounts of money.

Similar economic considerations may arise in a death that is not reported to the coroner-medical examiner either because it is not recognized that it falls into his jurisdiction, or the circumstances that might make it a coroner-medical examiner's case are too tenuous. The forensic implication may not be recognized or appreciated until long after the time of death. Autopsy in such cases may not provide "the final diagnosis," but it does permit a much more thorough foundation of both positive and negative findings on which an equitable, just, judicial decision may be based.

Conclusion

The needs of society and the law, for specialized medical knowledge in the investigation of certain types of death—most dramatically and notably, but by no means exclusively, homicides—have combined to develop the specialty of forensic pathology. Some of the needs are being increasingly felt in clinical medicine, not only in orthopedic surgery but in every type of medical practice. The paths of law cross all aspects of the practice of medicine, and it is through an increased awareness of this interplay that the clinician may best serve the needs of the patient, his family and society.

Forensic medicine should be a part of the training and basic medical armamentarium of every physician. The medical truth of every case, accurately observed, described, documented and presented as only a physician is capable of doing, provides that essential aspect that society requires.

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3. Wilentz WC: Workman's Compensation problems—Causal relationship on cardiac deaths. J For Sci 14:302-308, 1969

4. Curphy TJ: Role of the forensic pathologist in the medical certification, the modes of death. J For Sci 13:163-176, 1968

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Refer to: Whiting WB, Beyer RD: Workmen's compensation medico-legal interface—The questions of "arising out of employment in connection with employment" and the "presumption clause" (Information). Calif Med 119: 77-78, Sep 1973

Workmen's Compensation Medico-Legal Interface

The Questions of "Arising out of Employment in Connection with Employment" and the "Presumption Clause"

WILLIAM B. WHITING, MD
ROBERT D. BEYER, MPA
San Francisco

PHYSICIAN AWARENESS of some salient features of the California Labor Code will aid in the care of industrial patients. Misunderstandings frequently arise between physicians and workmen's compensation benefit administrators due to each using terminology unique to his discipline. Benefit administrators must strive to become sophisticated in the use and understanding of medical terminology. Physician familiarity with some of the terms unique to the workmen's compensation system will also facilitate more effective communication.

AOE-COE

The Law

The compensation insurance carrier, or other employer's representative, is charged with the responsibility of determining the employer's liability. This is necessary before acceptance of any claim for benefits. The terms used in this determination, by the workmen's compensation industry, are AOE (arising out of employment) and COE (in the course of employment). Both of these conditions must be met before an injury or illness is to be accepted as of an occupational or industrial cause.[1]

Discussion

The physician's report aids in the determination of employer's liability in two ways:

1. The history as given by the patient or his associates, or both; and
2. The medical opinion as to the appropriateness of the patient's complaint to the alleged incident or his occupation.

The recording of the initial history, before its possible alteration by extraneous influences, is most important in the fair determination of AOE-COE. The history, as obtained from the patient or his colleagues, can be used as a starting point by the benefit administrator in establishing the relationship of the occupation to the complaint. Direct quotation is frequently the most useful way of recording this history.

Medical facts (for example, signs, symptoms, diagnosis and prognosis) accompanied by the treating physician's opinion as to the occupational relationship, should be supported by the reasons for formulating this opinion.

It is then the benefit administrator's task to obtain any further information that seems necessary to make a fair determination of the employer's liability.

Presumption

The Law

Several specific employee groups within the State of California enjoy the "presumption clause" of the Labor Code.[2] The Legislature has deemed the risk of these occupations as justification for this liberal determination of the employer's liability. Specific public service occupations included in this clause are law enforcement officers and fire fighters (volunteer and paid). Any hernia, heart trouble, or pneumonia developing or manifesting itself in the above occupations is to be presumed to arise out of and in the course of employment (AOE-COE).[2] "Such hernia, heart trouble, or pneumonia so developing or manifesting itself in such cases shall in no case be attributed to any disease existing prior to such development or manifestation."[3]

For safety officers (for example, employees of

From the California State Compensation Insurance Fund, 525 Golden Gate Avenue, San Francisco.

Reprint requests to: W. B. Whiting, MD, Medical Officer, State Compensation Insurance Fund, 525 Golden Gate Avenue, San Francisco, CA 94101.

the Department of Corrections and state college campus guards) the presumption applies to heart trouble only.

Tuberculosis is presumed AOE-COE for all policemen, sheriffs and deputy sheriffs, and personnel of peace officer status in the State Criminal Identification and Investigation Bureau and the Bureau of Narcotics Enforcement.[4]

Discussion

The term *heart trouble* as used in the presumption portion of the Labor Code has been interpreted by the legal community in its broadest application. Heart trouble, by legal precedent, includes:

1. Rheumatic heart disease;
2. Luetic heart disease;
3. Congenital heart disease;
4. Arteriosclerotic heart disease;

and has recently been construed to include peripheral arteriosclerosis.[5]

The legal interpretation of the term *heart trouble,* then, includes all abnormalities involving the heart. The term, as used, is legal—not medical. Application of the presumption clause is being liberally construed to encompass more and more kinds of employment. For example, a teacher at a correctional facility has qualified for benefits covering open-heart operation for valvular damage existing from childhood due to rheumatic fever.

REFERENCES

1. California Labor Code Section 3600
2. California Labor Code Section 3212
3. California Labor Code Section 3212.5
4. California Labor Code Section 3212.2, 3212.5, 3212.6, 3212.7
5. Workmen's Compensation Appeals Board, 3-Civil No. 12848, final adjudication pending

Proposed CMA Constitutional Amendments

FOR ACTION IN 1974

Four Constitutional amendments were introduced in the 1973 House of Delegates. Under the terms of the Constitution, these amendments must lie on the table until the next regular meeting of the House of Delegates.

These proposed amendments are shown here for the information of the membership. In addition, the proposed Constitutional amendments are required to be printed in two issues of CALIFORNIA MEDICINE before they come before the House of Delegates for action.

* * *

ARTICLE IV, SECTION 6—BENEVOLENCE FUND

Introduced by: Council
Representing: Council
Author: John T. Saidy, MD

Constitutional Amendment 1-73
Committee G

Resolved: That Article IV, Section 6.—Benevolence Fund, be amended by deleting the words in brackets, and adding the words in italics, so that the section shall now read:

"At least [$1.00] *$0.50* out of the annual dues paid by each active member of the Association shall be allocated to the Physicians' Benevolence Fund, Inc., a Corporation, and shall be used for the purposes as set forth in that Corporation's Articles and Bylaws."

ACTION: Tabled for one year; to be acted upon at the 1974 meeting of the House of Delegates.

* * *

FORMATION OF NEW COUNCILOR DISTRICT

Introduced by: 11th District Delegation
Author: John R. Heckman, MD

Constitutional Amendment 2-73
Committee G

Resolved: That Article III, Part B, Section 10 of the CMA Constitution be amended as follows: (deletions in brackets, additions in italics)

Section 10.—Councilor Districts

There are [12] *13* Districts as follows:

District Number One, comprising San Diego and Imperial Counties.

District Number Two, comprising Riverside, San Bernardino, Mono and Inyo Counties.

District Number Three, comprising Orange County.

District Number Four, comprising the County of Los Angeles.

District Number Five, comprising Ventura, Santa Barbara and San Luis Obispo Counties.

District Number Six, comprising Alpine, Amador, Kern, Kings, Tulare, Fresno, Madera, Mariposa, Merced, Stanislaus, San Joaquin, Calaveras and Tuolumne Counties.

District Number Seven, comprising Monterey, San Benito, Santa Cruz, Santa Clara and San Mateo Counties.

District Number Eight, comprising San Francisco County.

District Number Nine, comprising Alameda County and Contra Costa County.

District Number Ten, comprising Marin, Solano, Napa, Sonoma, Lake, Mendocino, Humboldt and Del Norte Counties.

District Number Eleven, comprising Sacramento *and* El Dorado, [Placer, Nevada, Sierra, Yuba, Sutter, Yolo, Colusa, Glenn, Butte, Plumas, Tehama, Trinity, Shasta, Lassen, Modoc and Siskiyou] Counties.

District Number Twelve, *comprising Placer, Nevada, Sierra, Yuba, Sutter, Yolo, Colusa, Glenn, Butte, Plumas, Tehama, Trinity, Shasta, Lassen, Modoc and Siskiyou Counties.*

District Number Thirteen, consisting of any society which is not limited as to geographical area, or the area of which overlaps the area covered by one or more existing component societies;

such society and its members shall not be considered to be members of any other councilor district.

ACTION: Tabled for one year; to be acted upon at the 1974 meeting of the House of Delegates.

* * *

ARTICLE IV, SECTION 6—"BENEVOLENCE FUND"

Introduced by: Reference Committee "G"

Constitutional Amendment 3-73
Committee G

Whereas, the Benevolence Fund is now at sufficient size that it is self-supporting; and

Whereas, the addition of new monies to the Benevolence Fund is more properly placed in the immediate control of the House of Delegates as in the matter of dues; now, therefore, be it

Resolved: That Article IV, Section 6.—Benevolence Fund—be deleted in its entirety (deletion in brackets) as follows:

[At least $1.00 out of the annual dues paid by each active member of the Association shall be allocated to the Physicians' Benevolence Fund, Inc., a Corporation, and shall be used for the purposes as set forth in that Corporation's Articles and Bylaws.]

ACTION: Tabled for one year; to be acted upon at the 1974 meeting of the House of Delegates.

* * *

ARTICLE III, PART A, SECTION 1(d)—VOTING PRIVILEGES FOR SCIENTIFIC BOARD REPRESENTATIVES IN THE HOUSE OF DELEGATES

Introduced by: Council

Constitutional Amendment 4-73
Committee G

Resolved: That Article III, Part A, Section 1 (d)—House of Delegates composition shall be amended by deleting the words in brackets and adding the words in italics, so that this Subsection shall now read:

"(d) Ex officio, [without] *with* the right to vote, [eighteen (18)] *twenty-one (21)* members of the Scientific Board selected as provided in the Bylaws, and . . ."

ACTION: Tabled for one year; to be acted upon at the 1974 meeting of the House of Delegates.

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

AFFLERBAUGH, JACK KENNETH, Pomona. Died June 24, 1973 in Los Angeles, aged 62. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1939. Licensed in California in 1939. Doctor Afflerbaugh was a member of the Los Angeles County Medical Association.

⁂

BARNES, NORMAN J., Los Angeles. Died June 8, 1973 of cardiac infarction, aged 67. Graduate of University of Manitoba Faculty of Medicine, Winnipeg, 1928. Licensed in California in 1938. Doctor Barnes was a member of the Los Angeles County Medical Association.

⁂

BILON, LOUIS, Los Angeles. Died June 8, 1973 in Los Angeles of acute coronary occlusion, aged 76. Graduate of the University of Nebraska College of Medicine, Omaha, 1925. Licensed in California in 1927. Doctor Bilon was a member of the Los Angeles County Medical Association.

⁂

BOLAND, ARTHUR E., Los Angeles. Died July 20, 1973 in Los Angeles of heart disease, aged 87. Graduate of the University of Illinois College of Medicine, Chicago, 1909. Licensed in California in 1910. Doctor Boland was a member of the Los Angeles County Medical Association.

⁂

CAMMACK, BRAGG C., Hollywood. Died July 18, 1973 in Hollywood of heart disease, aged 78. Graduate of Baylor University College of Medicine, Houston, 1924. Licensed in California in 1936. Doctor Cammack was a member of the Los Angeles County Medical Association.

⁂

CUMMINGS, EDWARD CLARENCE, Oxnard. Died March 30, 1973 in Marina Del Rey of heart disease, aged 52. Graduate of Hahnemann Medical College and Hospital of Philadelphia, 1947. Licensed in California in 1948. Doctor Cummings was a member of the Ventura County Medical Society.

⁂

DAYTON, GORDON A., Arcadia. Died January 1, 1973 in Los Angeles, aged 58. Graduate of the University of Colorado School of Medicine, Denver, 1943. Licensed in California in 1947. Doctor Dayton was a member of the Los Angeles County Medical Association.

⁂

FALK, CHARLES C., JR., Eureka. Died July 13, 1973 in Portland, Oregon of heart disease, aged 71. Graduate of New York University College of Medicine, New York City, 1931. Licensed in California in 1932. Doctor Falk was a retired member of the Humboldt-Del Norte County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

FERRIER, PAUL ALEXANDER, JR., Los Angeles. Died July 9, 1973 in Los Angeles, aged 50. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1949. Licensed in California in 1951. Doctor Ferrier was a member of the Los Angeles County Medical Association.

⁂

HAMPTON, ROBERT GEORGE, Eureka. Died July 6, 1973 in Eureka, aged 50. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1948. Licensed in California in 1948. M.D. degree from California College of Medicine, 1962. Doctor Hampton was an associate member of the Humboldt-Del Norte County Medical Society.

⁂

HERZER, JULIO R., Los Angeles. Died December 19, 1972 in Hollywood of cerebral hemorrhage, aged 45. Graduate of Universidad Nacional de Buenos Aires, Facultad de Ciencias Medicas, 1951. Licensed in California in 1967. Doctor Herzer was a member of the Los Angeles County Medical Association.

⁂

JENKINS, KENNETH BAXTER, Oakland. Died June 28, 1973 in Carmel of injuries received in an automobile accident, aged 63. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1934. Licensed in California in 1934. Doctor Jenkins was a member of the Alameda-Contra Costa Medical Association.

⁂

JOHNSON, RUSSELL L., Paramount. Died January 8, 1973 in Lynwood of heart disease, aged 74. Graduate of the University of Illinois College of Medicine, Chicago, 1925. Licensed in California in 1926. Doctor Johnson was a member of the Los Angeles County Medical Association.

⁂

KEIG, WILLIAM C., Richmond. Died July 6, 1973 in Pinole of hepatic cirrhosis, aged 57. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1942. Licensed in California in 1942. Doctor Keig was a member of the Alameda-Contra Costa Medical Association.

⁂

KERLAN, MILTON, Beverly Hills. Died January 26, 1973 of heart disease, aged 71. Graduate of the University of Minnesota Medical School, Minneapolis, 1925. Licensed in California in 1931. Doctor Kerlan was a member of the Los Angeles County Medical Association.

⁂

LUSTER, HENRY H., Los Angeles. Died April 21, 1973 in New York City of complications following thoracic operation, aged 55. Graduate of Temple University

School of Medicine, Philadelphia, 1942. Licensed in California in 1948. Doctor Luster was a member of the Los Angeles County Medical Association.

⁂

MOTCHAN, LOUIS A., Los Angeles. Died February 24, 1973 in Los Angeles, aged 65. Graduate of Washington University School of Medicine, St. Louis, 1933. Licensed in California in 1937. Doctor Motchan was a member of the Los Angeles County Medical Association.

⁂

NICHOLUDIS, THOMAS N., Los Angeles. Died May 23, 1973 in Ann Arbor, Michigan of injuries received in a plane crash, aged 41. Graduate of Chicago College of Osteopathy, Chicago, 1959. Licensed in California in 1962. M.D. degree from California College of Medicine, 1962. Doctor Nicholudis was a member of the Los Angeles County Medical Association.

⁂

PAHL, BLYTHE W., Santee. Died July 7, 1973, aged 68. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1934. Licensed in California in 1934. Doctor Pahl was an associate member of the San Diego County Medical Society.

⁂

PIERCE, CHARLES HENRY, San Francisco. Died July 8, 1973 in San Francisco, aged 50. Graduate of Meharry Medical College, Nashville, 1950. Licensed in California in 1957. Doctor Pierce was an associate member of the San Francisco Medical Society.

⁂

PILLSBURY, STIRLING G., Long Beach. Died May 18, 1973 in Long Beach of cerebrovascular accident, aged 74. Graduate of Harvard Medical School, Boston, 1923. Licensed in California in 1923. Doctor Pillsbury was a member of the Los Angeles County Medical Association.

⁂

QUINN, ROBERT S., Santa Rosa. Died July 20, 1973 in Rio Vista of heart disease, aged 63. Graduate of the University of Oregon Medical School, Portland, 1935. Licensed in California in 1936. Doctor Quinn was a retired member of the Sonoma County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

REYNOLDS, JOHN G., Escondido. Died July 6, 1973 in Escondido, aged 45. Graduate of the University of Southern California School of Medicine, Los Angeles, 1955. Licensed in California in 1956. Doctor Reynolds was a member of the San Diego County Medical Society.

⁂

ROBERTSON, HUGH SCHUYLER, JR., San Mateo. Died July 14, 1973 in San Mateo, aged 53. Graduate of Cornell University Medical College, New York, 1944. Licensed in California in 1948. Doctor Robertson was a member of the San Mateo County Medical Society.

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Acute Renal Cortical Necrosis

Variable Course and Changing Prognosis

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Three cases of acute bilateral renal cortical necrosis, each with a different clinical course, are discussed. One patient spontaneously recovered renal function after prolonged oliguria. This case should be added to the small number of similar case reports in the literature. The second patient recovered adequate renal function temporarily, but eventually required chronic hemodialysis and renal transplantation. There was pathological evidence of progression from focal to massive cortical necrosis. The third patient never regained renal function, but is well after dialysis and transplantation.

The influence of modern theories of pathogenesis of the disease, and increased availability of dialysis, are discussed in relation to the initial prognostic assessment of the patient with cortical necrosis.

RENAL CORTICAL NECROSIS has been studied extensively since it was first described by Juhel-Renoy in 1886. It occurs most frequently following a complication of pregnancy,[1-3] particularly abruptio placentae.[2-4] Other precipitating events of an obstetrical nature are toxemia of pregnancy, retention of a stillborn fetus, and septic abortion.[2,3] The most common non-obstetrical cause in adults is sepsis.[2,5] Other causes are burns, shock, and neoplasm.[5] Cortical necrosis was the cause of approximately 2 percent of all cases of acute renal failure in a large series.[6]

The most characteristic clinical feature of the disease is anuria. Flank pain, gross hematuria, fever, severe anemia and hypotension have also been observed.[5] Calcification of the cortex is an occasional radiologic finding.[7] The usual course of severe cases, particularly in earlier studies, was progression to terminal renal failure.[1-4,7] Recovery of renal function following prolonged oliguria is rare.[1,9-11] One such case is presented herein; and in two other cases the patients are living and well following hemodialysis and transplantation.

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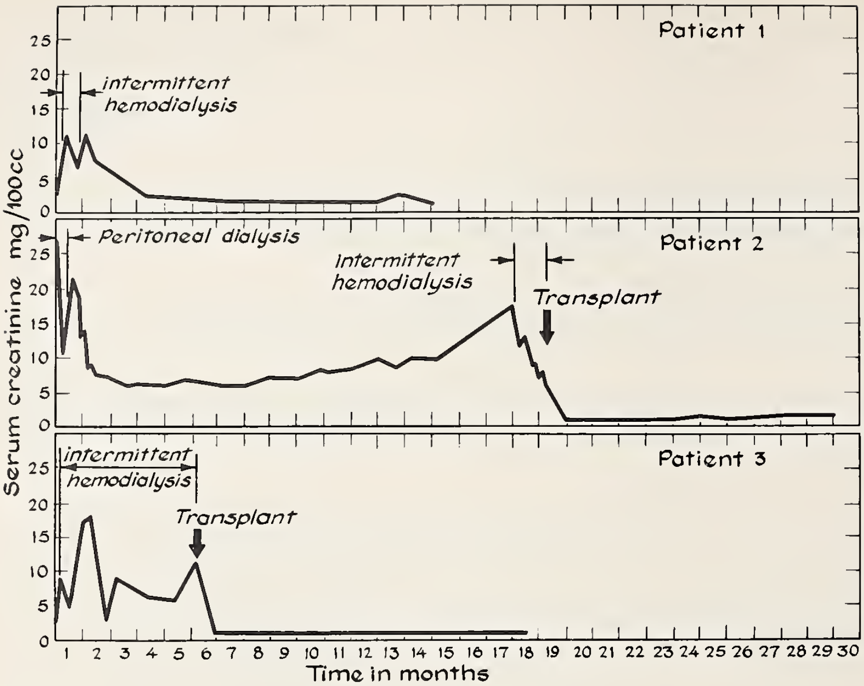

Chart 1.—The clinical course of each patient as reflected by the serum creatinine. Note the spontaneous and persistent improvement of Patient 1, the temporary improvement and later deterioration of Patient 2, and the absence of any spontaneous improvement of Patient 3.

Summaries of Cases

Patient 1. A 28-year-old multipara in her eighth week of pregnancy entered Stanford University Hospital for an elective saline-induced abortion 5 August 1969. She said she had not had previous renal disease and hypertension. Blood pressure and urinalysis on admission were within normal limits. Immediately following the abortion the patient became anuric. Profuse vaginal hemorrhage was treated by uterine curettage, fibrinogen, and transfusions of whole blood. Several hours after the operation the prothrombin time was 27 percent, partial thromboplastin time 75 seconds, fibrinogen 70 mg per 100 ml, and the platelet count 80,000 per cu mm. Microangiopathic changes were noted on a peripheral blood smear. Disseminated intravascular coagulation secondary to amniotic fluid embolism was suspected, and heparin therapy was begun. On the following day the patient was dyspneic; she complained of flank and left anterior chest pain. The blood pressure was 86/64 mm of mercury. Bilateral costovertebral angle tenderness was noted, as was diffuse ecchymosis. She remained anuric. The serum creatinine was 3 mg per 100 ml. The urine was grossly bloody and the protein content 3+. The sediment contained innumerable red blood cells, a moderate number of renal tubular epithelial cells, and a few granular casts. No hemoglobin casts were seen. On the basis of the clinical evidence, acute cortical necrosis was felt to be the most likely diagnosis.

By the third day of illness the fibrinogen level, partial thromboplastin time and prothrombin time had returned to normal. Heparin was discontinued. By the fourth day symptoms had disappeared and blood pressure had returned to normal. During the next two weeks the hematocrit dropped gradually from 29 percent to 18 percent. It returned to 26 percent (without transfusion) by the time of discharge on the 12th day. Anuria persisted and hemodialysis was required. The ecchymosis cleared.

On the 24th day of illness, urine output increased and dialysis was discontinued. The serum creatinine decreased from 11.1 mg per 100 ml on that day to 2.1 mg on the 100th postoperative day (Chart 1).

One year later the patient was asymptomatic, and physical examination was normal. The hematocrit was 36 percent and a peripheral blood smear normal. The blood urea nitrogen (BUN) was 30 mg and the serum creatinine 1.7 mg per 100 ml. Nephrotomograms revealed kidneys 11.5 cm in length without calcification. Examination of kidney tissue obtained by percutaneous biopsy revealed that a band of fibrous tissue had replaced most of the cortex; however, the remaining glomeruli appeared normal. These findings were interpreted as representing healed cortical necrosis.

Two years following operation the patient was still asymptomatic and serum creatinine was 1.1 mg per 100 ml.

Comment

The initial clinical manifestations of this case of cortical necrosis were fever, gross hematuria, flank pain and anuria. The hypoprothrombinemia, thrombocytopenia, and microangiopathic hemolytic anemia were consistent with disseminated intravascular coagulation, possibly precipitated by an amniotic fluid emolism. A long period of anuria ensued. Although renal biopsy was not performed during the acute episode, the histologic features one year later were entirely consistent with previous acute cortical necrosis. The contribution of heparin to the successful management of this patient is conjectural, although previous studies have suggested a beneficial effect of heparin therapy in disseminated intravascular coagulation and related syndromes.[9,12] The limitations of percutaneous biopsy in establishing the diagnosis and the extent of acute cortical necrosis are demonstrated by this case. Had the biopsy specimen contained only fibrous tissue, complete cortical destruction might have been suspected. If it had contained only normal glomeruli, the diagnosis could not have been established.

Patient 2. A 17-year-old girl was first admitted to Stanford University Hospital in acute renal failure in January 1969. She had been quite healthy until three weeks before admission, when she experienced chills, fever, mild sore throat and periumbilical cramps. Weakness, nausea, and vomiting prompted her to consult a physician two days before admission. During the three days before she entered the hospital she was oliguric.

On 5 January 1969, a seizure prompted admittance to hospital. On arrival, she was somnolent and had generalized hyperreflexia. The blood pressure was 128/84 mm of mercury. The fundi were normal and there were no petechiae. A grade 3/6 apical systolic murmur was present. The hematocrit was 26 percent. The urine sediment contained 10 to 15 erythrocytes and leukocytes per high-power field, occasional oval fat bodies and finely granular casts. The serum creatinine was 28 mg per 100 ml and the BUN 255 mg per 100 ml. The ASO titer was 166 Todd Units. The platelet count, prothrombin time, clot retraction and bleeding time were within normal limits. A lupus erythematosus preparation was negative.

Peritoneal dialysis was instituted and somnolence disappeared. The daily urine output was less than 70 ml for four days. A low-grade fever persisted for four days. Dialysis was discontinued five days after admission. The next day the urine output began to climb steadily. Serum creatinine reached a high of 20.4 mg per 100 ml, then gradually decreased to 6.3 mg at the time of discharge, two months after admission (Chart 1).

Nephrotomograms done one week after admission demonstrated approximately normal renal size. The right kidney was 12.4 cm long and the left kidney 13.7 cm. A repeat examination six weeks later showed bilateral decrease in length, to 9.5 and 10.0 cm. There was no calcification.

Open renal biopsy was performed during the eighth week of illness. Microscopic examination showed extensive areas in which all the glomeruli were hyalinized or necrotic, and all the tubules either were replaced by fibrous tissue or showed acute and chronic inflammatory cell invasion. Elsewhere the tubules were hypertrophied and the glomeruli exhibited focal basement membrane thickening, with focal proliferative and necrotizing changes. These changes were interpreted as representing focal cortical necrosis.

Following discharge of the patient, renal function remained stable for nine months, but then began to deteriorate; by the 17th month the serum creatinine had risen to 17.1 mg per 100 ml (Chart 1). During this period several urine cultures and lupus erythematosus preparations were negative. During the 17th month chronic hemodialysis was begun.

Bilateral nephrectomy and splenectomy were performed during the 19th month. Renal sections were typical of massive cortical necrosis (Figure 1). Only a very thin rim of cortex was present, with hyalinized, closely packed glomeruli (Figure 2). In the remainder of the kidney interstitial fibrosis, tubular atrophy and dilatation, and foci of chronic inflammation were observed. Twenty months after the onset of illness the patient received a renal transplant with her father as donor. During 14 months of observation after transplantation she has been free of symptoms, and results of physical examination were always within normal limits. Serum creatinine was 1.1 mg per 100 ml, and the creatinine clearance 54 ml per minute.

Comment

The findings on renal biopsy early in the patient's course were compatible with focal cortical necrosis. When the kidneys were removed 18

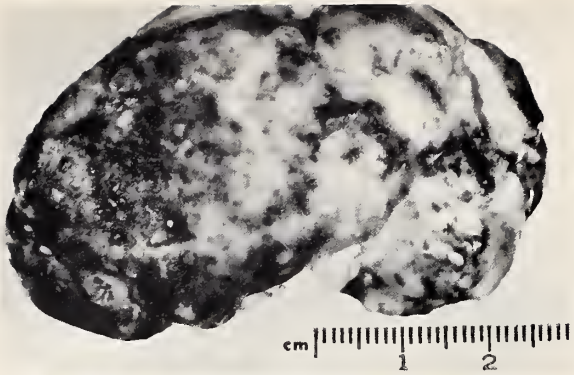

Figure 1.—Nephrectomy specimen (Patient 2).

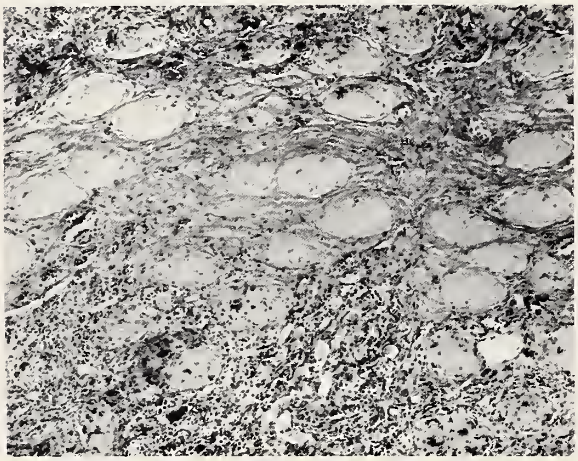

Figure 2.—This portion of the nephrectomy specimen is a subcapsular cortical area with total glomerular hyalinization and tubular loss. Note the inflammatory infiltrate at the edges of this area (Patient 2).

months later the findings were typical of the massive or "gross" form of the disease. The cause of the cortical necrosis is obscure. Progressive renal failure following partial recovery of renal function has been reported in acute cortical necrosis,[9,15] but has never been adequately explained. In this case there was pathological documentation of progression from focal to massive cortical necrosis, although there was no evidence of chronic disseminated intravascular coagulation.

Patient 3. A 39-year-old woman experienced severe vaginal bleeding and abdominal cramps on 30 November 1969, during the seventh month of pregnancy. Abruptio placentae was diagnosed, and an emergency cesarean section was performed at another hospital. Complete abruption was confirmed at operation and a stillborn fetus was delivered. The blood pressure during operation reached a low of 118/84 mm of mercury (compared with 184/114 on admission). Following the operation the patient was anuric. On the first postoperative day, the serum creatinine was 3.1 mg per 100 ml. The fibrinogen level was normal. On the second day she was transferred to Stanford University Hospital.

On arrival the patient appeared drowsy, but was in no distress. She did not complain of flank pain. The blood pressure was 185/110 mm of mercury. Examination of the fundi revealed A-V nicking and two flame-shaped hemorrhages. Basilar rales, generalized hyperreflexia, and a trace of pedal edema were present. That evening the serum creatinine was 7.4 mg per 100 ml. Prothrombin time, partial thromboplastin time, and fibrinogen level were within normal limits. There was no clot lysis. The platelet count was 65,000 per cu mm and remained depressed for four days. Antinuclear antibodies and lupus enythematosus preparations were negative. The antistreptolysin-O titer was 166 Todd units. By the third postoperative day the serum creatinine had risen to 9 mg per 100 ml. Hemodialysis was instituted. Severe oliguria persisted for three weeks. Although urine output then increased slightly, the patient never recovered an adequate degree of renal function (Chart 1). Several transfusions were required for severe anemia (hematocrit 15 percent) during this stay in hospital.

On the 40th postoperative day she was discharged, and dialysis was continued on an outpatient basis. Nephrotomograms on the 60th day demonstrated that the left kidney was 9.3 cm long and the right kidney 9.5 cm. This represented a 2 cm decrease bilaterally in a period of two months. There was no evidence of calcification.

On the 122nd day the patient was re-admitted for nephrectomy and renal transplantation. The kidney had a thin, granular, knobby cortex. The left kidney was 8.2 cm in its longitudinal axis, the right 8.4 cm. Microscopic examination revealed extensive fibrosis and cortical hyalinization. Approximately 90 percent of the glomeruli were destroyed. The pathological diagnosis was massive cortical necrosis.

On the 138th day a related-donor renal transplantation was performed. Excellent renal function was observed immediately afterward. Sixteen months after transplantation the serum creatinine is 1.0 per 100 ml and the creatinine clearance 71 ml per minute.

Comment

In this case there were certain typical characteristics of massive cortical necrosis, including prolonged anuria and oliguria, relative hypotension, severe anemia, and a decrease in kidney size. The irreversible loss of intrinsic renal function was representative of a more common clinical course than was noted in the first two cases.

The pathologic features in the kidneys in this case as in the two others were consistent with Sheehan and Moore's[4] criteria for cortical necrosis and did not resemble those of any other known renal disease.

Discussion

Previous reviews[4,5,8,9] have emphasized that the usual course of renal cortical necrosis with prolonged oliguria is permanent loss of renal function. A second course and then spontaneous recovery of adequate renal function after prolonged oliguria, has been described, but this is an extremely rare event.[1,3,9-11] The patient in the first of the three cases herein reported should be added to the very small number of patients who have regained normal renal function.

A third course, gradual progression to end-stage renal failure after partial recovery of function, is illustrated by the second of the three cases. This course has received no attention in previous reviews,[4,5,8] although it is evident that with increased use of dialysis to support patients throughout their initial period of oliguria, it should occur with increasing frequency.

Earlier reviews[4,5,8] also emphasized adequate renal function as being essential to survival. Cortical necrosis was universally attributed to prolonged, intense vasoconstriction. In animal experiments vasoconstriction had been shown to cause cortical necrosis. Many investigators[16-18] now propose that renal cortical necrosis is the clinical equivalent of the generalized Shwartzman reaction, whereas others feel that the disease results from a combination of the two events.[3] In the Shwartzman reaction the central pathogenic event is disseminated intravascular coagulation, which may result from a wide variety of insults. Many of these, such as neoplasm, overwhelming sepsis, shock or severe trauma, are lethal regardless of their effect on renal function. Others, such as obstetrical complications, carry a relatively good initial prognosis.

Now that hemodialysis and transplantation are generally available, it is clear that eventual recovery of renal function should not be considered the most important prognostic factor in cortical necrosis. Recovery from the event which has precipitated the disseminated intravascular coagulation will determine the fate of the patients.

Since spontaneous recovery of renal function seven weeks after the onset of the disease has been reported,[9,13,19] dialysis for at least two months before resort to nephrectomy is recommended. It has been demonstrated[19] that a small surviving population of juxtamedullary nephrons can gradually undergo adaptive changes which enable them to sustain a remarkable degree of renal function. Since the finding of extensive cortical necrosis on needle biopsy[9,14] does not rule out the survival of such nephrons, the patient should be given opportunity to recover some degree of renal function before nephrectomy is considered.

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Congenital Postero-Lateral Diaphragmatic Hernia in Children

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Congenital diaphragmatic hernia must be seriously considered in the differential diagnosis of acute respiratory distress in neonates as well as in older infants who present with chronic progressive gastrointestinal and respiratory symptoms. An x-ray film of the chest is mandatory and is almost always diagnostic. Immediate nasogastric decompression of the stomach, with simultaneous fluid and electrolyte replacement and prompt surgical intervention offers the patient the best chance of survival.

CONGENITAL DIAPHRAGMATIC HERNIAS requiring surgical correction are not uncommon in the neonatal and infancy period. The majority of these hernias are of the foramen of Bochdalek type and usually present as acute respiratory emergencies in the newborn. The operative mortality in this group varies from 30 percent to 50 percent[1-3,7,10] despite advances in pediatric anesthesia and surgical techniques. A second distinct but less well recognized clinical group consists of older infants with diaphragmatic hernias beyond the neonatal period, who present with failure to thrive, intermittent vomiting, or progressive respiratory difficulty. Usually in such cases elective repair has excellent results.

Experience with four patients with congenital diaphragmatic hernia who were successfully operated upon in a recent six-month period prompted us to review the records of six other surgically treated patients, and the ten cases form the basis of this report.

Clinical Material

The records of 14 patients with congenital diaphragmatic hernia seen at the Kern General Hospital between 1956 and 1972 were reviewed. In ten cases of postero-lateral diaphragmatic hernia surgical repair was carried out. One case of a foramen of Morgagni hernia was managed conservatively. An additional three cases were found in the autopsy records for the same period. In two of the three autopsy cases, the lesion was of the Bochdalek type. In the third there was congenital absence of the left hemidiaphragm. These three patients required immediate resuscitation following delivery and none survived more than an hour after birth.

In the ten cases of Bochdalek hernia that were

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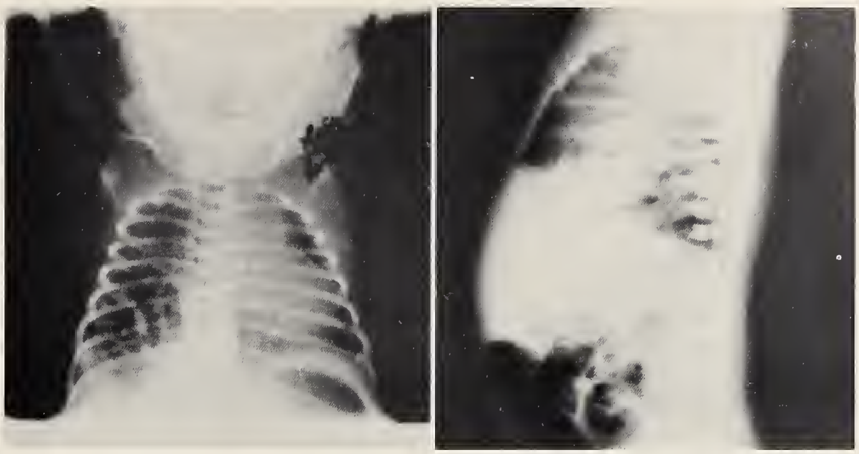

Figure 1.—Roentgenograms of the chest show herniation of bowel and liver into the right hemithorax with compression of the lung and mediastinal shift toward the left, in a newborn infant with respiratory distress (Case 5).

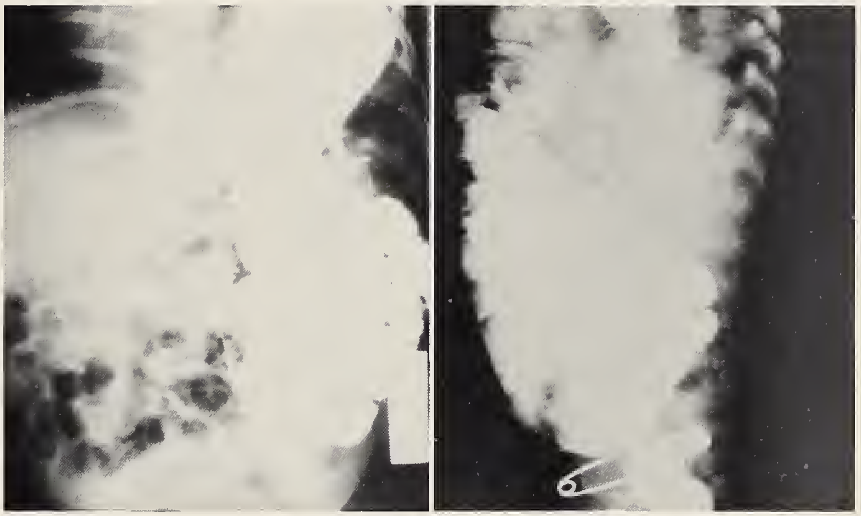

Figure 2.—Upper gastrointestinal radiographs show stomach and intestines containing contrast material in the left thoracic cavity in a three-month-old boy with failure to thrive and intermittent vomiting (Case 7).

surgically treated, five of the patients were males and five females. They can be divided into two groups, based on their ages and the presenting symptoms. The first group consists of five neonates whose ages ranged from three to twenty-one hours. All except one were full term and of normal birth weight. They all presented with cyanosis and acute respiratory distress, and in all cases a pronounced mediastinal shift away from the involved side was noted roentgenographically (Figure 1). Three of the hernias were on the left side and two involved the right side with a herniated liver and a thoracic kidney. The small and large intestines were consistently present in all the hernias, although a sac could not be demonstrated in any of them. A transabdominal approach was used in all the cases. Except in the case of a premature baby (Case 4), the ipsilateral lung became fully expanded within 48 hours after operation. There were no operative deaths, even though two of the neonates had associated congenital anomalies (an omphalocele and a ventricular septal defect).

In the second group of five infants who had surgical correction of diaphragmatic hernia, the age range was from four weeks to four months. All had a history of intermittent vomiting and episodes of cyanosis since birth. Two had not attained normal weight. In no case was the operation done in acute surgical emergency, and in two cases complete upper gastrointestinal radiographs were obtained to confirm the diagnosis (Figure 2). Two patients had significant mediastinal displacement toward the normal lung (Cases 6 and 7) due to obstruction of the gastric outlet. The displacement was dramatically relieved by nasogastric suction. The hernia was on the left side in four cases and on the right side in one. A sac was present in two cases. The repair was accomplished through the abdominal approach in three cases, and through a combined thoracoabdominal approach in the other two. In all five patients, chest x-ray films immediately after operation showed complete re-expansion of the ipsilateral lung. The postoperative course was uneventful in all cases.

Discussion

The formation of the diaphragm by fusion of its various components between the eighth and tenth week of fetal life results in the division of the coelomic cavity into its abdominal and thoracic compartments. A developmental anomaly or arrest in the course of its fusion could conceivably result in a variety of diaphragmatic defects: (1) foramen of Bochdalek (persistent pleuroperitoneal canal); (2) foramen of Morgagni (subcostosternal defect); (3) eventration; (4) absence of central tendon; and (5) hiatal hernia. The most common herniation is through the foramen of Bochdalek since the postero-lateral portion of the diaphragm is the last part to close. The hernia is more common on the left side (85 to 90 percent)[4] because the right hemidiaphragm completes its closure before the left,[5] and because the liver protects the right hemidiaphragm from pressure of the returning intestines during the tenth week until after closure is complete.[4] Bilateral herniation is rare.[6] Although it is certain that the diaphragmatic defect is congenital, herniation of the abdominal viscera may not occur until later on in life.[8,9]

The incidence of congenital diaphragmatic hernia is about 1:7,000 live births.[10] The male to female ratio is two to one.[11]

The defect occurred on the left side in seven of the ten patients operated on for the Bochdalek type of hernia in this study. The small and large intestine were involved in all cases and a hernial sac was present in two of them. In 10 to 15 percent of patients a hernial sac can be demonstrated.[4] The kidney was in the thoracic cavity in two cases, the spleen in three cases, and a lobe of the liver in two. Malrotation, which has been reported to occur in about 30 percent[12] of patients with diaphragmatic hernia, was described in three cases. Major associated congenital anomalies were

TABLE 1.—*Data on Ten Cases in Which Operation Was Done for Correction of Bochdalek Diaphragmatic Hernia*

Case No.	*Age*	*Sex*	*Presenting symptoms*	*Diagnosis*	*Diaphragmatic Defect*	*Hernia contents*	*Hernia sac*	*Malrotation*	*Associated anomaly*	*Follow up*
1. . . .	21 hours	F	Respiratory Distress	Chest x-ray	Left Posterolateral, 3cm × 1cm	Small bowel and colon	none	none	none	Well at 5 mo
2. . . .	10 hours	M	Respiratory Distress	Chest x-ray	Left Posteromedial, 3cm × 2cm	Small bowel and colon	none	none	none	Well at 4 mo
3. . . .	21 hours	F	Respiratory Distress	Chest x-ray	Right Posterolateral, 7cm × 7cm	Kidney, small bowel and colon	none	present	omphalocele	Well at 3 yr
4. . . .	12 hours	M	Respiratory Distress	Chest x-ray	Left Posterolateral, 4cm × 4cm	Spleen, small bowel and colon	none	none	ventricular septal defect	Well at 5 yr
5. . . .	3 hours	F	Respiratory Distress	Chest x-ray	Right Posterolateral, 6cm × 2cm	Liver, small bowl and colon	none	none	none	Well at 1 mo
6. . . .	4 months	M	Failure to thrive, fever, vomiting	Chest x-ray, U.G.I.	Left Posterolateral	Kidney, spleen, stomach, small and large bowel	present	present	none	Well at 13 yr
7. . . .	3 months	M	Failure to thrive, fever, vomiting	Chest x-ray, U.G.I.	Left Posterolateral	Liver, spleen, stomach, small and large bowel	present	present	none	Well at 2 yr
8. . . .	4 weeks	F	Vomiting and cyanotic spells	Chest x-ray	Right Posterolateral	Small bowel and colon	none	none	none	Well at 14 yr
9. . . .	6 weeks	M	Vomiting and cyanotic spells	Chest x-ray	Left Anterolateral	Small bowel and colon	none	none	none	Well at 2 yr
10. . . .	3 months	F	Vomiting and dyspnea	Chest x-ray	Left Posterolateral	Small bowel and colon	none	none	none	Well at 3 mo

encountered in two surgical patients (Cases 3 and 4). Two of the three patients examined at autopsy had an atrial septal defect and one had a severe coarctation of the aorta.

The classic triad of dyspnea, dextrocardia and cyanosis was present in all five neonates. In the infancy group, the predominant symptoms were failure to gain weight, vomiting and progressive respiratory embarrassment. Breath sounds were described as subdued or absent on the involved side in all the patients. The diagnosis was made in all cases by plain roentgenograms of the chest and was confirmed by barium swallow in two older infants.

Immediate nasogastric suction, replacement of fluids and electrolytes, correction of acidosis, and administration of humidified oxygen were part of the routine preparation of the patient for operation. In the critically ill newborn with severe respiratory distress, endotracheal intubation with respiratory support provided by the technique of Gregory et al[13] and careful monitoring of the pH and blood gas changes by umbilical artery catherization are recommended. Following reduction of the abdominal contents, re-expansion of the ipsilateral lung occurred within 48 hours in all except one premature neonate, whose lung did not fully expand until a week after operation. The involved lungs in the three autopsy cases in which the patient died within an hour after birth and before a diagnosis could be made, were found to be hypoplastic. Hypoplasia of the ipsilateral lung has been reported to occur in congenital diaphragmatic hernia[7,10-12,14] and has been produced experimentally in fetal lambs following the creation of a diphragmatic hernia *in utero*.[15] Pulmonary function studies in infants done several years after successful surgical repair have shown a residual defect in those whose lungs were originally hypoplastic.[16] Since the hypoplastic lung is not capable of immediate expansion even in pressures causing rupture of the alveoli, vigorous attempts at forceful expansion of the collapsed lung during and after operation must be discouraged, for it may lead to contralateral tension pneumothorax.

The abdominal approach was used in eight patients, while in two the initial incision had to be extended into the chest because of difficulty in the reduction and repair of the hernia. Reduction of the displaced viscera may be facilitated by slipping a catheter through the hernia defect into the chest to allow for equalization of the negative intrathoracic pressure, in the manner of C. H. Mayo.[17] The diaphragmatic defect was closed directly in all cases. Gastrostomy was performed in one patient. It is important to inspect the entire intestine carefully for patency and to ascertain that there is no malrotation or duodenal obstruction (from Ladd's bands) before closing the abdomen. In no case was it necessary to create a temporary ventral hernia or silo to accommodate the reduced, displaced viscera, although this may be essential in selected cases to obviate restrictive ventilatory problems and reduced venous return due to extremely tight abdominal closure.

Intrapleural chest tubes connected to waterseal drainage were used in six patients. None of the infants required prolonged respiratory support, which partly accounts for the favorable result in this series, since respiratory insufficiency and hypoxia is a recognized major cause of mortality especially in the neonatal group with pulmonary hypoplasia.

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Whole Body Skeletal Scintiphotography in the Detection of Occult Metastatic Breast Carcinomas

G. BRUCE HOPKINS, MD, *and* KAI A. B. KRISTENSEN, MD, *La Jolla*

Whole body skeletal scintiphotography was carried out in a series of 111 breast cancer patients. The results of scintiphotography were compared with the results of roentgenography and with the diagnostic usefulness of serum alkaline phosphatase levels and the presence or absence of bone pain. In 27 percent of cases, lesions were first identified with the scintiphotos. When lesions were present on both scintiphotos and roentgenograms, involvement generally appeared greater on the scintiphotos. Two false negative studies were recorded. Sixty-seven percent of patients with early metastasis—that is, those with positive scintiphotos and negative roentgenograms—were asymptomatic. Serum alkaline phosphatase levels were normal in 38 percent of those with early skeletal involvement. Skeletal scintiphotography is superior to other commonly employed techniques used to assess bone metastasis in breast carcinoma.

How CANCER of the breast is treated depends largely on the extent of the disease at the time of discovery. Radical operation is employed on the premise that the tumor has not spread beyond the breast and regional lymph nodes. As the skeleton is the most frequent site of distant extension,[1,2] skeletal scintiphotography is of primary importance in determining the stage of the disease. Roentgenograms are inadequate in this regard.[3]

Bone-seeking radionuclides localize in the skeleton and reflect the metabolic activity of the bone mineral. Pathologic conditions characterized by increased osteogenic activity or localized increased osseous perfusion may be visualized by scintiphotography. Though the scintiphoto locates the site of disease, it is nonspecific and should be accompanied by appropriate roentgenograms. In a cancer patient positive scintiphotographs without

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roentgenographic evidence of bone disease are considered presumptive of early metastasis.

Strontium-85 (^{85}Sr) has been the most commonly employed bone imaging agent; however, certain problems are inherent in its use, mainly its long physical half-life of 65 days. Approximately 50 percent of the administered dose is tightly bound to the skeleton, resulting in appreciable radiation. Because of low count rates obtained with acceptable doses of ^{85}Sr, scanning must be done at low speeds, making routine skeletal surveys impractical. Attempts to screen asymptomatic patients have generally been limited to the thoracic and lumbosacral spine and pelvis.[4,5] Obviously occult metastastic lesions at other sites will be missed. The use of certain short-lived radionuclides can obviate this problem. The larger trace doses permissible with these agents increase the count rates, permitting faster scanning speeds and hence routine whole body surveys.

Skeletal scintiphotography with two short-lived nuclides was carried out in a large group of breast cancer patients, and the accuracy and sensitivity of this method was compared with those of other techniques commonly employed to assess possible bone metastasis.

Methods and Materials

The series was made up of 111 patients with biopsy-proven breast carcinoma. The majority had radical or modified radical surgical procedures and all patients had been observed at regular intervals. The scans and roentgenograms had all been obtained within three weeks of each other. The presence or absence of bone pain was recorded at the time of scintiphotography.

The clinical records of the patients were reviewed and the serum alkaline phosphatase values, when available, were tabulated. The phosphatase determinations were performed in the hospital laboratory by the method of Bessey, Lowry and Brock.[6]

TABLE 1.—*Comparison of Scintiphotos with Roentgenograms and Serum Alkaline Phosphatase Activity*

	No.	*Percent*
Scintiphotos and Roentgenograms		
Scintiphoto positive, x-ray positive	48	43
Scintiphoto negative, x-ray negative ...	31	28
Scintiphoto positive, x-ray negative	30	27
Scintiphoto negative, x-ray positive	2	2
Scintiphotos and Phosphatase Activity		
Scintiphoto positive, Alk. P'tase elevated	47	62
Scintiphoto positive, Alk. P'tase normal	29	38
Scintiphoto negative, Alk. P'tase elevated	0	0

The two short-lived nuclides employed were carrier-free Fluorine-18 (^{18}F) and Technetium-99m (^{99m}Tc) complexed with either a polyphosphate or diphosphonate carrier.[7,8] The half-life of ^{18}F is 1.8 hours, that of ^{99m}Tc six hours. Fluorine-18 was used in 80 patients and the ^{99m}Tc complex in 31 patients. Technetium-99m has only recently been introduced for use in bone imaging and is the superior agent. Its low monoenergetic gamma emission of 140 keV is ideally suited for high resolution studies with either a gamma camera or rectilinear scanner, whereas ^{18}F produces annihilation photons of 511 keV that render high resolution studies difficult with conventional scintillation cameras.

The principal instrument used was a scintillation camera. The whole body was surveyed to include the axial skeleton, skull and extremities. With ^{18}F a pinhole collimator was employed. A rectilinear scanner was occasionally used over areas of questionable activity.

Results

The results of scintiphotography, roentgenograms and serum alkaline phosphatase determinations are summarized in Table 1. The scintiphotos and roentgenograms correlated in 79 cases (71 percent. In 30 cases (27 percent) lesions were shown on scintiphotos but not on roentgenograms. Metastasis in these cases was confirmed by subsequent roentgenographic change, by biopsy (Figures 1 and 2), by relief of osseous pain by radiation therapy, or at autopsy. Scintiphotography was negative or equivocal in two patients with lesions on roentgenograms.

Serum alkaline phosphatase determinations obtained within two weeks of scintiphotography were available on 86 of the 111 patients. Of these, ten were excluded because of possible co-existing liver disease as demonstrated by an abnormal liver scan or biopsy, or abnormal liver chemical determinations. Of the remaining patients, 29 (38 percent) with positive scintiphotos had normal serum alkaline phosphatase levels.

Twenty (67 percent) of the 30 patients with positive scintiphotos and negative roentgenograms were asymptomatic. One or more metastatic sites were asymptomatic in 14 patients (29 percent) with lesions present on both scintiphotos and roentgenograms.

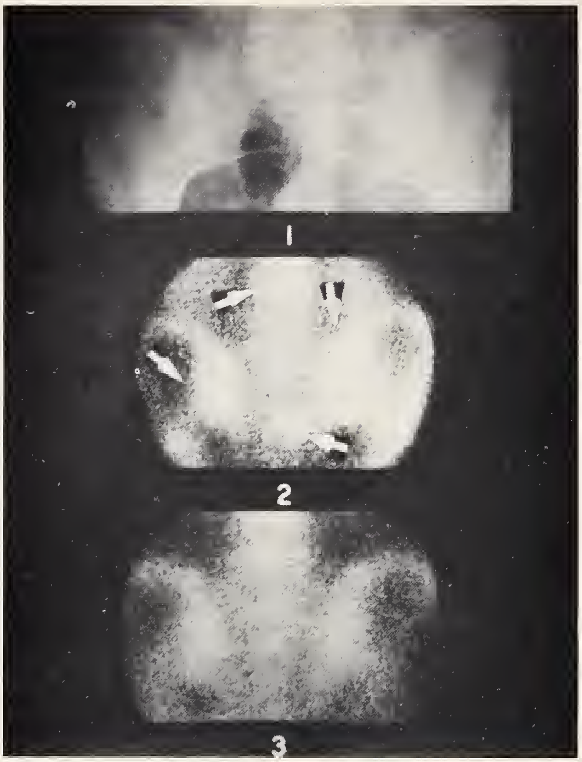

Figure 1.—Example of metastatic pelvic lesions first detected by the scintiphoto. The patient's first roentgenogram (1) was negative. However, scintiphotos (2) obtained at the same time demonstrated metastasis. A normal pelvic scintiphoto (3) is included for comparison.

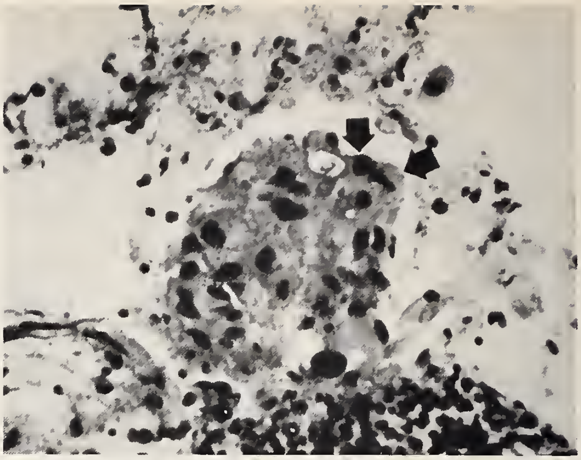

Figure 2.—Biospy of one of the iliac lesions present in the scintiphoto in Figure 1, showing metastatic breast carcinoma (hematoxylin and eosin × 250).

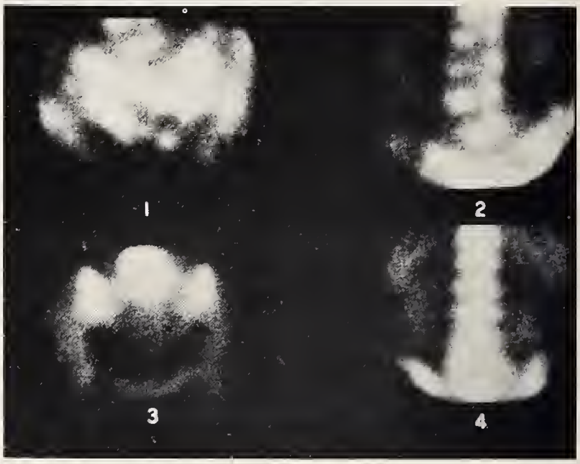

Figure 3.—Extensive metastasis in the pelvis (1) and lumbar spine (2) in an asymptomatic patient. A normal pelvis (3) and lumbar spine (4) are included for comparison.

Discussion

In this series of 111 patients, scintiphotography with short-lived nuclides proved more sensitive than roentgenograms in detecting early skeletal metastasis. Moreover, when metastastic lesions were present on both scintiphotos and roentgenograms, the involvement often appeared greater on the scintiphotos. The greater diagnostic acuity of scintiphotography is in its ability to reflect the early dynamic changes occurring in response to tumor. Roentgenograms show only the net structural change which occurs, both destructive and reparative.[9] Not until 30 percent to 50 percent of an involved bone is destroyed does a lesion become evident on roentgenograms.[3]

In the present series, scintiphotos were interpreted as negative or equivocal in two cases in which roentgenograms were positive. In one of the two, scanned with ^{18}F, involvement of the axial skeleton was uniform and diffuse, so that no one area appeared unduly active when compared with other areas. The scintiphotographs in that case had been considered equivocal. The lesion in the other case was osteolytic and had not elicited any reparative bone activity. Osteolytic metastasis has been reported as a cause of false negative Strontium scans.[5,10]

In 16 (53 percent) of the 31 patients studied with ^{99m}Tc, skull lesions in addition to other bone metastasis were demonstrated. In ten patients (32 percent) with early metastasis, the skull was the first site of involvement. A similar frequency of skull lesions was not evident with the ^{18}F scintiphotos, nor on a previous study of ^{18}F scintiphotographs reported from this hospital.[11] The increased frequency is believed to be ascribable to the technically superior scintiphotos obtained with ^{99m}Tc. Our limited experience suggests that routine whole-body surveys with ^{99m}Tc may reveal a previously unrecognized predilection for skull metastasis in breast cancer.[2]

Scintiphotographs also proved more sensitive than serum alkaline phosphatase determinations. The serum alkaline phosphatase was normal in 38 percent of patients with metastasis demonstrable on scintiphotos. Elevated serum alkaline phosphatase levels were more commonly observed in patients with late metastasis—that is, those with lesions observed on both scintiphotos and roentgenograms. In no case did elevation of serum phosphatase precede a positive scan or roentgenogram. While the serum phosphatase may be of value in indicating late hepatic metastasis, it would appear to be of questionable worth in detecting early skeletal involvement.

Bone pain was the least sensitive indicator of metastasis. Sixty-seven percent of patients with early metastasis, as determined by positive scintiphotos and negative roentgenograms, were asymptomatic. In some cases the asymptomatic involvement was quite extensive (Figure 3).

While skeletal scintiphotography is a highly sensitive indicator of bone disease, it is not specific for tumors and may yield abnormal results in a variety of conditions. This is particularly true with diseases affecting reparative bone activity. In our experience, non-neoplastic conditions causing positive scintiphotos include osteomyelitis, rheumatoid spondylitis, recent fractures, Paget's disease, hyperostosis frontalis, arthritides, regional osteoporosis, aseptic necrosis and postoperative healing. When scintiphotos are positive, appropriate roentgenography should be done to rule out other causes of altered bone metabolism.

Scintiphotos on the majority of patients in the present series were not obtained until more than four months after operation. Of 16 patients studied within two months of operation, two with positive scintiphotos had negative lymph nodes in the resected specimens. In two others, lymph involvement was limited to one axillary node in one case and to three nodes in the other.

The results of this study indicate that skeletal scintiphotography is the procedure of choice in following patients with carcinoma of the breast. Roentgenograms, serum phosphatase levels or a history of bone pain all proved less sensitive or accurate than scintiphotography. Bone imaging is not only of importance in screening patients with known carcinomas, but is also indicated before resort to radical operation on patients suspected of breast cancer.

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Specialty Conference

Moderator

GEORGE A. BRAY, MD

Discussants

DAVID L. RIMOIN, MD, PhD
MARK A. SPERLING, MD
ROBERT H. FISER, MD
RONALD S. SWERDLOFF, MD
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This symposium is based on a Teaching Conference held November 27, 1972 at Harbor General Hospital, Torrance

The Obese Diabetic

A Symposium on New Developments

Genetics of Diabetes Mellitus

DAVID L. RIMOIN, MD, PhD*

DIABETES MELLITUS is a major public health problem that affects approximately 2 percent of the American population. Although an enormous amount of research has been done on this disease in the past 50 years, its pathogenesis is still largely unknown. Hereditary factors are generally accepted to be of great etiologic importance, but there is little agreement as to the nature of the genetic mechanisms involved.[1-3]

Evidence in favor of a large genetic component is based primarily on studies of the familial aggregation of the disease, studies of twins and studies of population, using markers such as clinical diabetes, abnormalities in glucose tolerance tests, the secretion of insulin and thickening of the basement membrane.[1,4-12] Regardless of the marker used, be it clinical diabetes or abnormal glucose tolerance, there is a significantly greater prevalence of abnormality among the relatives of diabetic persons than among similar relatives of those who do not have the disease. In almost none of these studies, however, were individual family units examined, nor was there any attempt to define different genetic forms of diabetes. Although the evidence derived from studies of familial ag-

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gregation and twins leaves no doubt as to the etiologic importance of genetic factors in diabetes, the mode of inheritance of the diabetic trait(s) is unknown.[1,2]

During the past several decades every possible mode of genetic transmission has been proposed, and objections have been raised to all of them. This disagreement is due in part to a number of obstacles with which the geneticist is confronted in his attempts to unravel this problem. These include vast differences in the definition of an affected person or an affected relative. For example, to meet the criteria in some studies an affected person must have significant clinical symptoms of the disease, while in others only a mildly abnormal glucose tolerance test is accepted. The clinical variability, variability in the age of onset of the disease, and susceptibility to environmental factors present further difficulties to the delineation of an affected person. Furthermore, the high prevalence of the disease in the population raises questions of relative genetic fitness. The most important impediment to genetic analysis, however, is the lack of knowledge concerning the basic defect in diabetes. Because of this, there is no certain method for detecting prediabetic persons—that is, those with the mutant genotype who have, as yet, no signs of carbohydrate intolerance.

Although the mode of transmission of the diabetic genotype is obviously in question, many investigators have accepted the autosomal recessive hypothesis as fact and have based their definition of "prediabetics" on this assumption. If such were the case, all offspring of two diabetics must possess the diabetic genotype. However, only about 50 percent of such offspring have been found to be affected, irrespective of the marker used to define diabetes.[13-16] These observations may be the result of several factors. First, there may be incomplete penetrance of the gene. Second, diabetes may not be inherited as a simple, autosomal recessive trait, but rather as a dominant or polygenic trait. Multiple factors are certainly involved in the variability of normal blood sugar levels but polygenic inheritance as a cause of clinical diabetes mellitus has not been proven. Indeed, recent studies by Steinberg et al[17] have demonstrated bimodality in blood sugar concentrations in populations with a high prevalence of the disease. Third, diabetes mellitus may be a heterogeneous group of disorders—that is, a number of distinct disorders caused by different gene mutations at different loci, each of which results in carbohydrate intolerance.[1,2]

Evidence in favor of the hypothesis of heterogeneity includes (a) clinical variability in the disease, as exemplified by the differences between juvenile and maturity onset diabetes, (b) ethnic variability in the clinical and metabolic features of diabetes apparently not directly related to environmental factors, (c) biochemical heterogeneity as exemplified by both insulinopenic and hyperinsulinemic forms of diabetes, and (d) the occurrence of abnormal glucose tolerance in over 30 distinct genetic syndromes due to mutations at many different loci, as well as to several chromosomal aberrations[1] (Table 1). Furthermore,

TABLE 1.—*Genetic Syndromes Associated with Glucose Intolerance*

Alstrom syndrome
Ataxia telangiectasia
Cockayne syndrome
Cystic fibrosis
Friedreich's ataxia
Glucose-6-phosphate dehydrogenase deficiency
Type I glycogen storage disease
Hemochromatosis
Huntington's chorea
Hyperlipemia, diabetes, hypogonadism, and short stature
Hyperlipoproteinemia III
Hyperlipoproteinemia IV
Hyperlipoproteinemia V
Isolated growth hormone deficiency
Laurence-Moon-Biedl syndrome
Lipoatrophic diabetes
Muscular dystrophy
Myotonic dystrophy
Ocular hypertension induced by dexamethasone
Optic atrophy and diabetes
Optic atrophy, diabetes insipidus, and diabetes mellitus
Hereditary relapsing pancreatitis
Photomyoclonus, diabetes, deafness, nephropathy, and cerebral dysfunction
Pineal hyperplasia and diabetes
Acute intermittent porphyria
Pheochromocytoma
Prader-Willi syndrome
Retinitis pigmentosa, neuropathy, ataxia and diabetes
Schmidt syndrome
Werner syndrome
Turner syndrome
Klinefelter syndrome
Down syndrome

TABLE 2.—*Risk of Development of Diabetes When a Parent, Sibling or Child Is a Diabetic*

Age of Nondiabetic (years)	*Risk of Diabetes (percent)*
0 – 19	< 1
20 – 39	1
40 – 59	3
60 +	10

(After Simpson, NE[5])

TABLE 3.—*Genetically Transmitted Syndromes with Obesity*

	Rodent	*Man*
Dominant .	Yellow Mouse	Achondroplasias
Recessive .	Obese Mouse	Laurence-Moon-Biedl
	Fatty Rat	
	Diabetes Mouse*	
	Adipose Mouse*	
Polygenic .	Japanese KK Mouse	
	New Zealand Obese	

*Allelomorphic.

genetic heterogeneity has been well documented in mice, being associated with at least four simply inherited disorders due to mutations at different loci, as well as being present in high frequency in a number of distinct strains which have been developed by selection and inbreeding (Table 3). All of this evidence points toward the possibility that diabetes represents a heterogeneous group of disorders and that hyperglycemia is a non-specific manifestation of a variety of different mechanisms. Indeed, hyperglycemia may be no more specific than anemia, and the use of diet, oral hypoglycemic agents or insulin may be as non-specific as a blood transfusion.

Theoretically, there are a number of ways in which the mutation of a gene could affect insulin synthesis, secretion, transport or action so as to produce carbohydrate intolerance. Some of these possibilities include a structural mutation in the insulin molecule, a defect in the enzyme which cleaves insulin from proinsulin, decreased synthesis or secretion of a normal insulin molecule, glandular hypoplasia or degeneration, peripheral unresponsiveness to the actions of insulin, or circulating antagonists to insulin action. It is likely that many, if not all, of these mechanisms do produce abnormal glucose tolerance, and future research into this symptom-complex must provide a means of identifying the specific pathogenetic mechanism operating in each diabetic patient before accurate genetic counselling can be given.

Since the mode of inheritance of diabetes is still in question, accurate genetic counselling is impossible. Various tables listing the risk of an individual's inheriting the diabetic genotype have been published, based on the assumption that diabetes is inherited as a simple autosomal recessive trait[20] or on the basis of a statistical analysis of morbid risk figures, calculated from limited clinical experience.[21] Simpson[3,21] has constructed relative risk figures for the development of clinical diabetes among first degree relatives of diabetics, based on data obtained from questionnaires on a large population (Table 2). The risk of a given relative's developing diabetes varies with the age at onset of diabetes in the proband. If diabetes developed in the proband at less than 20 years of age, the risk figures should be approximately doubled, except for persons over 60 years of age. If there is more than one parent, sibling or child who is diabetic, the risks are also approximately doubled. These relative risk figures are, of course, approximations and must be related to the age-specific risk for diabetes in the specific population from which the person being counselled derives. Although these risk figures allow the counselor the satisfaction of quoting a number to the person he is counselling, the inexactness should be made clear.

There has recently been some controversy on whether or not diabetics should be allowed to marry one another and have children. The World Health Organization[22] advises that they should be counselled not to marry each other, or that if they do they should not have children. The WHO bases this advice on the presumption that "conjugal diabetics may increase the number of diabetic offspring and perhaps determine the appearance of diabetics at earlier ages." Edwards[23] pointed out the fallacy of this advice and claimed that these recommendations would probably not increase the number of subsequent diabetics but would simply influence their allocation. It is apparent that, with our limited knowledge concerning the genetics of diabetes, it is difficult to offer informative genetic counselling to an individual couple, and foolhardy to attempt eugenic measures.

Obesity

Genetic factors also play a role in the transmission of certain forms of obesity.[19] Among experimental animals, distinct forms of hereditary obesity have been described with different modes on inheritance (Table 3). The yellow obese mutation of mice is transmitted as a dominant trait. In the yellow pure form, homozygosity for the mutation is lethal (A^y), but among two alleles in a mottled yellow coat color, obesity can be present (A^{iy}; A^{vy}) without being lethal. In four distinct disorders of rodents, obesity is inherited as an autosomal recessive trait.

The most widely known example of this group is the obese mouse, ob/ob (synonym, obese-hyperglycemic mouse). Although the obesity is not present at birth, the animal becomes corpulent within the first three or four weeks of life and continues to gain weight thereafter, reaching a body weight which can be more than three times that of its siblings. "Adipose" is a second mutation in the mouse resulting in recessively inherited obesity. Matings between carriers of the gene for adipose and carriers of the gene for obese do not produce fat offspring, indicating that these two genes (ob and ad) are not allele. A third mouse, "diabetes" (db), is also fat, but in addition suffers from diabetes. Twenty-five percent of the offspring from matings between carriers of ad and db genes are obese, indicating that these two mutants are allele. The fatty rat is another mutation in the rodent in which obesity is transmitted as an autosomal recessive trait. Polygenic inheritance of obesity has also been described in two inbred strains of mice called New Zealand Obese and the Japanese KK mouse. The variety of rodents with genetically transmitted obesity suggests that obesity is a heterogeneous trait in man.[23]

That genetic factors also pay a prominent role in the development of human obesity is shown in the results of twin studies and in studies of families of obese and lean persons.[24] In one study, a number of anthropological measurements were made on 57 pairs of twins. Weight had the widest variability among these measurements, but was usually within a small difference even when the environmental background had been dissimilar. Thus, environmental factors play a greater role in determining body weight than in determining the length of the arm, overall height, or such dimensions as the circumference of the head or neck. Comparison of identical and fraternal twins has shown much more variability among the fraternal twins and siblings than between the pairs of identical twins. Indeed, only 2 percent of the identical twins differed in weight by more than 12 pounds in contrast to 25 percent of the dizygotic twins. The importance of genetic factors is also apparent in examining the offspring of various types of marriages. When two "lean" persons marry, only rarely are the offspring obese. The offspring of the overweight population tended to be overweight but with a greater variability than was observed among the offspring of lean marriages.[25] Although such findings could be ascribed to environmental differences, they are likely due in part to differences in genotype upon which any environmental factors operate.[26]

Control of Insulin Secretion

MARK A. SPERLING, MD*

INSULIN OCCUPIES the central role in the modulation of the body's fuel metabolism.[27] The introduction of the radioimmunoassay procedure[28,29] permitted extensive investigations of the factors controlling endogenous insulin secretion. However, because secreted insulin first enters the portal circulation and is extracted by the liver to a variable extent, peripheral plasma levels cannot be equated with secretion. To delineate more precisely the relationship between stimulus and response, a number of approaches, including pancreatic perfusion, pancreatic slices or isolated pancreatic islets, have been utilized. This review aims to be a synthesis of known facts primarily as they pertain to humans. Other reviews have recently appeared.[30,31] Throughout, the term *insulin concentration* refers to levels measured by radioimmunoassay. It should be remembered that immunoreactivity cannot be equated with biological activity. For example, the biosynthesis of insulin, a dipeptide molecule linked by disulphide bridges, involves a third connecting peptide chain. This precursor, proinsulin, will be measured as insulin in most immunoassay procedures, although it is structurally distinct, and biologically less active.[32]

Fortunately, except in patients with insulinoma, proinsulin accounts for only some 10 to 20 percent of measurable immunoreactive insulin, and hence alterations in insulin levels following physiological manipulation *in vivo* or *in vitro* do not in probability reflect insulin secretion.

Basal Insulin

Although the beta cell of the pancreas is capable of responding to a stimulus, it also maintains a basal level of insulin secretion. In a human, following an overnight fast, insulin levels do not fall to zero, but are maintained within a defined normal range, declining even further in parallel with glucose during a prolonged fast.[33] Glucose thus appears to be involved in the direct feedback mechanisms for basal insulin levels. However,

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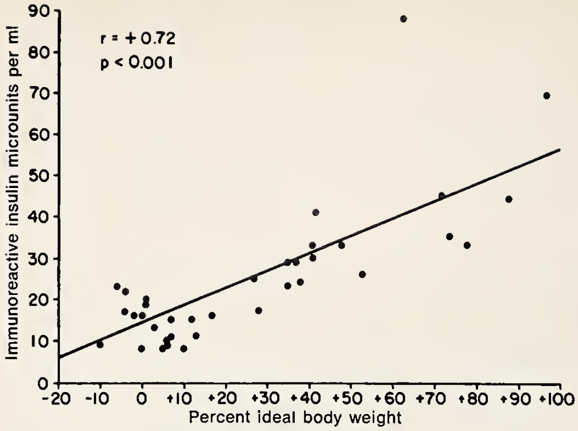

Chart 1.—Correlation of fasting serum immunoreactive insulin and obesity expressed as percent of ideal body weight. (Reproduced with permission from Bagdade et al.[35])

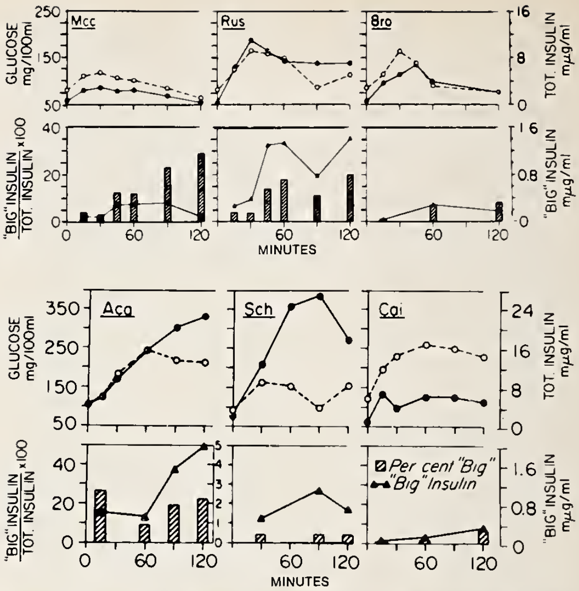

Chart 2.—Big and little insulin during a glucose tolerance test in lean and obese subjects. The upper panel represents the glucose and immunoreactive insulin values during an oral glucose tolerance test. The bars represent the values for the big insulin. Presumably the "big insulin" represents proinsulin.[149]

other potential factors which may be involved include the products of intermediary metabolism, such as amino acids, fatty acids and ketones, as well as a variety of hormones such as glucagon, growth hormone, cortisol, and the catecholamines, all of which are characterized by fluctuation during the fast. These potential factors are discussed in subsequent sections. Of all the factors, obesity seems to be the most constant.[34-36] As will be discussed in detail by Dr. Bray in a subsequent section, the degree of obesity influences the basal and stimulated insulin levels irrespective of blood glucose level (Chart 1).

During fasting, subjects of varying weights reduce basal insulin levels proportionately and weight reduction to normal is associated with a return toward normal basal insulin levels[36] (Chart 2). It has been suggested that the basal secretion is regulated by the rate of glucose metabolism or by continuous high carbohydrate intake.[37] A hypothalamic glucoreceptor for modulating insulin secretion has also been proposed.[38]

Nutrient Regulation of Insulin Secretion

Since insulin is involved in the channeling of the body's energy needs, it is not surprising that nutrients profoundly affect insulin secretion.

Glucose

Following a bolus of intravenous glucose, there is an acute release of insulin, reaching peak levels between 3 and 4 minutes and rapidly returning to basal after approximately 10 minutes. The magnitude of the insulin response to this rise and fall depends upon the size of the input—that is, the amount of glucose—and the preexisting basal insulin secretion, itself modified by factors such as obesity and hormone status. Prolonging the infusion (for up to 20 hours) results in a second rise of insulin; and ultimately a new steady state is attained, in which both glucose and insulin are elevated. An additional pulse of glucose at any time during this steady state, results in an additional immediate release of insulin. These findings have given rise to the concept that insulin is released from two pools,[39-46] with the pool which releases acutely representing preformed insulin. Support for this concept comes from studies on perfusion of rat pancreas, where puromycin, an inhibitor of protein synthesis, inhibits the delayed response but has no effect on the immediate acute response.[40]

Studies of the pancreatic islet by electron microscopy tend to support this concept.[47] These studies have suggested that glucose initiates the synthesis of proinsulin in the endoplastic reticulum. Proinsulin is then transported to the Golgi apparatus, where the connecting peptide is split off, leaving insulin. The insulin granules are then "packaged" in smooth membranous sacks and discharged into the cytoplasm, where they become associated with the microtubular-microfilamentous system of the cell and gradually make their way to the cell surface where they can be discharged by a process called emiocytosis. Calcium is believed to influence this process by causing contraction of the microtubules and thereby hastening the migration of granules to the cell surface. The acutely releasable pool would thus represent insulin granules already close to the surface, while the secondary rise could be explained by newly synthesized insulin. Glucose appears to be the major substrate capable of eliciting the secondary response. In addition, it appears that the acute response is the determining factor in maintaining normal glucose tolerance.[42,43]

A quantitative relationship between the glucose concentration and insulin secretion has been demonstrated in a number of *in vitro* systems, including pancreatic slices from rabbit and rat,[48,49] and isolated islets.[50,51] In many of these systems, (a) 50 to 100 mg per 100 ml of glucose is necessary to stimulate insulin release above baseline, and (b) maximal insulin secretion occurs at concentrations of approximately 300 mg per 100 ml. Human beings seem to follow the same principles. For example, glucagon does not stimulate insulin when the blood glucose is less than 50 mg per 100 ml.[52,53]

The manner by which glucose causes the secretion of insulin is not entirely defined. There is evidence that the beta cell membrane contains a specific receptor for glucose which may trigger insulin release independent of concurrent glucose utilization.[54] However, there is also evidence that a product or products of glucose metabolism may be involved in secretion of the insulin. Thus, 2-deoxyglucose, a non-metabolizable analogue of glucose, which enters the beta cells and inhibits phosphohexose isomerase, also inhibits insulin secretion.[55] Mannoheptulose, a seven-carbon sugar which competitively inhibits the phosphorylation of glucose, inhibits the secretion of insulin in rats *in vivo* and *in vitro*.[56-58] Similarly, glucosamine inhibits phosphorylation and insulin secretion.[58] Thus, it appears that glucose must be phosphorylated and further metabolized before inducing insulin release. Mannose and fructose, which are metabolized by pathways similar to glucose but less preferentially so, exert lesser effects on the release of insulin.[53,59] Galactose, which is not metabolized by islets, does not stimulate insulin secretion.[48-58] Glucose metabolism via the pentose phosphate pathway may be important in insulin release, since xylitol, ribitol and ribose stimulate insulin release from pancreatic islets, even in the presence of mannoheptulose or 2-deoxyglucose.[60]

TABLE 4.—*Amino Acid Stimulation of Insulin Secretion*

Amino Acid	*Relative Potency (Percent)*
10 amino acids	100
Arginine	86
Lysine	64
Leucine	34
Phenylalanine	32
Valine	12
Methionine	11
Threonine	│ <10 but >1
Isoleucine	│ <10 but >1
Tryptophan	↓ <10 but >1
Histidine	1
Protein plus glucose	Synergistic

Augmentation of the Glucose Signal

If glucose acts as a primary signal by interacting with a specific cell membrane glucoreceptor, it follows that a second messenger is required to initiate insulin secretion by the beta cell. Cyclic acid mucopolysaccharide (AMP), the ubiquitous second messenger of mammalian systems, has an established role in the process of insulin release.[61-66] Theophylline and caffeine, which slow the breakdown of cyclic AMP by inhibiting phosphodiesterase, enhance the initial response to intravenous glucose. Various ions also are required for insulin secretion. Calcium is essential for the stimulation of insulin secretion by glucose and tolbutamide.[67-69] Magnesium does not appear to be essential if calcium is present.[98] Potassium stimulates insulin release in the absence of glucose.[69] However, these studies have been performed *in vitro*, and their role *in vivo* is, with some exceptions, inferential.

Free Fatty Acids and Ketone Bodies

Free fatty acids and ketone bodies result in release of insulin following infusion into animals.[70] Studies in man are less convincing. Intravenous administration of acetoacetate or betahydroxybutyrate do not appear to cause a rise in insulin.[71] However, medium chain triglycerides administered orally do increase insulin levels.[72]

Amino Acids

The association of hypoglycemia and hyperinsulinemia following ingestion of leucine by infants led to a systematic study of the effects of amino acids on insulin secretion.[73] A group of ten amino acids given together was the most potent stimulus *in vivo*. Individual amino acids varied in their potency for insulin stimulation, with arginine be-

TABLE 5.—*Control of Islet Hormones by Nutrients and Gut Hormones*

	NUTRIENT			*GUT HORMONES*		
				Protein Responsive		*Glucose Responsive*
HORMONE	*Glucose*	*Amino Acid*	*Free Fatty Acid*	*Pancreozymin*	*Gastrin*	*Secretin*
Insulin	↑	↑	↑	↑ ↑	↑ ±	↑
Glucagon	↓	↑	↓	↑ ↑		↓

ing most effective and isoleucine least effective. These data are summarized in Table 4. The potency of amino acids as a stimulus to the release of insulin is independent of their effects on gluconeogenesis.[74] Amino acid-stimulated secretion of insulin is also demonstrable *in vitro.*[75] *In vivo,* the insulin response to amino acid is augmented by the simultaneous administration of glucose.[76,77] Infusion of small doses of amino acids results in release of insulin from the acute pool. However, constant high dose infusion of amino acids can also result in the release of insulin from the chronic pool.

Gut Hormones

Throughout this discussion we have referred to the insulin-releasing properties of intravenously infused test substances. However, in man, oral glucose results in higher peripheral levels of insulin and lower glucose values than an equivalent amount of intravenous glucose.[78] That intestinal hormones may be involved in the secretion of insulin was first suggested in 1906.[79] It is now known that secretin, pancreozymin and gastrin directly stimulate the release of insulin.[80,81] In addition, so-called gut glucagon, a factor present in acid alcohol extracts of intestinal mucosa which cross-reacts with most antisera to pancreatic glucagon, also has insulogenic properties.[82] The insulogenic properties of intestinal hormones are summarized in Table 5. Some of these intestinal hormones also promote the release of glucagon, itself a potent insulogenic hormone. Thus, the effect of intestinal hormones may be both direct and indirect via glucagon. It seems likely that the intestinal hormones, responding to the intake of nutrients, signal the release of insulin from the acute pool. The secretion of insulin would thus precede and anticipate the absorption of nutrients and, thereby, prevent initial hyperglycemia followed by reactive hypoglycemia. Indeed, it has been suggested that a defect in the enteric signal for insulin may be the defect in patients with maturity onset diabetes, where insulin responses to oral glucose are characterized by an initial delay.[42,43,52]

Nervous Control of Insulin Secretion

Sympathetic. Insulin secretion is modulated by sympathetic activity involving alpha and beta adrenergic receptors.[83-86] Thus, stimulation of alpha-adrenergic receptors, as occurs with epinephrine and norepinephrine, inhibits insulin secretion to a variety of stimuli. This inhibition involves the acutely releasable pool without altering basal secretion. The effects can be simulated by the infusion of the beta blocker propanolol. Conversely, alpha adrenergic blockade with phentolamine, or infusion of a beta stimulator such as isoproterenol, enhances insulin release in response to glucose. This entire system is closely integrated with the generation of cyclic AMP, since aminophylline administration can overcome propanolol blockade.[86] Recently, the type of beta receptor responsible for insulin secretion has been defined as the beta two type.[87] In man, stress is associated with the release of endogenous catecholamines which result in glucose and free fatty acid mobilization while inhibiting insulin release. Thus, a steady supply of fuel becomes available for the fight-or-flight reaction. The demonstration that the blunted release of insulin is associated with exercise, with surgical operation and with burns is further testimony of the physiological significance of this system.[88-91] The reduction of glucose tolerance in patients with pheochromocytoma has a similar mechanism.[92] Finally, the recently reported reduction of glucose tolerance and delayed insulin responses following the chronic administration of L-dopa may also have a similar basis[93] (Table 6).

Parasympathetic. Whereas sympathetic stimulation inhibits insulin release, most studies suggest that parasympathetic stimulation enhances the secretion of insulin both *in vivo* and *in vitro.*[94-98]

TABLE 6.—*Autonomic Control of Insulin Secretion*

Agent	*Insulin Release*
Epinephrine	Decreased
Norepinephrine	Decreased
Epinephrine plus Phentolamine or Phenoxygenzamine	Increased
Isoproterenol	Increased
Isoproterenol plus Propanolol	No Effect
Propanolol	Decreased
L-Dopa	Decreased
Acetylcholine	Increased
Methacholine	Increased

In addition, ganglionic blockade by pempidine inhibits insulin response to glucose and results in a diabetic pattern of glucose tolerance in humans.[99] Thus, integrated neural activity constantly modulates insulin responsiveness to a given stimulus. The autonomic control of insulin secretion is summarized in Table 6.

Hormones

Glucagon. A rise in plasma immunoreactive insulin following the intravenous administration of glucagon was first demonstrated by Samols and Marks.[100] This has been repeatedly confirmed in man and animals both *in vivo* and *in vitro*.[101-107] Evidence suggests that the effects of glucagon are mediated by activation of adenyl cyclase.[108] It has been pointed out that many of the gut hormones which stimulate the release of insulin also cause the release of glucagon. The juxtaposition of the alpha and the beta cells of the islet may make endogenous glucagon, a key stimulator of endogenous insulin secretion in certain circumstances. While this role of glucagon is not established, it should be pointed out that glucagon does not promote insulin secretion *in vivo* when blood glucose is less than 50 mg per 100 ml.

Growth Hormone. Persons with congenital growth hormone deficiency tend to have subnormal insulin levels, both in the basal state and following glucose stimulation.[109,110] Treatment of these persons with growth hormone restores insulin release to normal.[110] In patients with acromegaly, basal as well as stimulated insulin levels are increased.[111,112] Growth hormone, therefore, appears to be involved in insulin secretion both in the basal and the stimulated state, probably by increasing insulin synthesis and storage. These stimulatory effects of growth hormone on the secretion of insulin are antagonized by the diabetogenic effect of the growth hormone at the peripheral level.

ACTH and Adrenal Steroids. Excess corticosteroid, whether endogenous or exogenous, results in increased levels of insulin in the basal state and following stimulation.[113,114] These effects are counterbalanced by a state of insulin resistance at the periphery. Carbohydrate tolerance only becomes reduced when insulin reserve is impaired. This fact is the basis for the cortisone-primed glucose tolerance test used in the detection of diabetes. Glucocorticoids added to the pancreas *in vitro* do not stimulate the secretion of insulin.[48] However, pancreas from adrenalectomized animals does display decreased insulin responsiveness to glucose.[115]

In primary hyperaldosteronism glucose tolerance is impaired.[116] This most likely results from hypokalemia. As was previously indicated, potassium infusion can cause enhanced insulin release *in vitro* while potassium depletion in animals results in glucose intolerance and reduced insulin responses.[117]

Sex Steroids

Estrogens increase basal and stimulated levels of insulin. However, estrogen therapy results in impaired glucose tolerance by mechanisms which may involve hormonal and other insulin antagonists.[118,119] Progesterone does not alter basal insulin levels but does appear to enhance the release of insulin.[120] The impaired carbohydrate tolerance observed in pregnancy may be partially the result of these hormones, but it correlates best with chorionic sommatomammotropin, a placental hormone which has immunologic and biological similarities to growth hormone, and prolactin.[121]

Thyroid

Thyroxine *in vitro* has no direct effect on insulin release. However, pancreatic tissue from thyroidectomized animals has decreased release of insulin, and pre-treatment with thyroid hormone *in vivo* restores normal responses.[55,122] In humans, hyperthyroidism is associated with impaired insulin responses to hyperglycemia.[114,123]

Serotonin

Insulin release in patients with the carcinoid syndrome is impaired, and returns to normal following therapy of the primary tumor.[124] Methysergide maleate, a serotonin antagonist, enhances insulin response.[125] Thus, like the catecholamine, serotonin inhibits insulin secretion directly.

Summation

In normal man, insulin secretion is constantly modulated by the state of nutrition, by the hormonal milieu and by autonomic impulses. The ingestion of nutrients, principally carbohydrate and protein, produces intestinal hormonal signals which prime and initiate insulin release by the beta cell. The interaction of glucose with a specific beta cell receptor augments or may separately induce the release of preformed insulin. This sequence involves the cyclic AMP system, beta adrenergic receptors and ions, principally calcium. Subsequent glucose metabolism within the beta cell provides energy for the further synthesis and release of insulin. The synthesis of insulin involves the formation of a precursor, proinsulin.

Defects or excesses of individual components in this complex integrated system can account for abnormalities in glucose tolerance or insulin secretion such as are seen, for example, in obesity, pheochromocytoma or acromegaly. In juvenile diabetes, the capacity for insulin secretion in response to any stimulus is almost totally abolished, though basal insulin levels remain essentially normal. In maturity onset diabetes, the capacity to secrete insulin in response to a stimulus remains, but the response is qualitatively or quantitatively diminished. This diminution is due to either a defect in the signal or the ability of the beta cell to perceive and act on that signal, or to peripheral antagonists of the biological actions of insulin.

New Developments in Diabetes Obesity and Insulin Resistance

GEORGE A. BRAY, MD*

HUMAN OBESITY is accompanied by increased levels of insulin. This was first suggested by the finding of hypertrophied beta cells in the islets of Langerhans in 13 of 19 obese patients at autopsy[126] and by the abnormalities in glucose tolerance which occur in many corpulent persons.[127-131] With the development of a radioimmunoassay for the detection of insulin, it became possible to document the increased concentrations of insulin in obesity.[28,132] It is now generally agreed that the fasting level of immuno-reactive insulin is higher in the serum of obese patients than of lean subjects.[133-136] Of importance is the fact that the insulin levels are correlated with body fat. This is illustrated by the data of Bagdade and his collaborators where a positive correlation between the level of insulin and the percentage of excess weight was readily demonstrable (Chart 1). With weight reduction, fasting levels of insulin returned toward normal.[36,137]

In addition to the increased fasting levels of insulin which accompany obesity, obese persons have a greater rise in insulin than do normal persons in response to many provocative agents. Thus, the administration of glucose to adults[133-141] or children,[142-145] or the administration of L-leucine,[146] of glucagon[147] or of tolbutamide,[148] is accompanied by a pronounced hyperinsulinemia in the obese patient which is substantially greater than is observed in normal people. If the increase in insulin during the various provocative tests is expressed as a percentage increase over basal concentrations of insulin, however, there is little or no difference in response between obese and lean persons.[35] Hence the magnitude of the insulin response in overweight persons is related primarily to the higher level of basal insulin in such persons. Concentrations of plasma insulin in fasting obese subjects are often elevated without change in the levels of circulating glucose.[136] These observations raise two important questions: (1) By what mechanism does obesity produce hyperinsulinemia; and (2) By what mechanism does the body prevent a drop in glucose in the face of increased circulating levels of insulin?

Insulin Secretion. Several possible mechanisms can be invoked to explain the hyperinsulinemia of obesity. The first is that the insulin measured by immunological methods is not biologically active and that in reality neither the turnover nor the production of glucose or of insulin is altered. This possibility received support following the discovery of proinsulin.[32] The work of Steiner and his collaborators has shown that the biosynthesis of insulin in the pancreatic beta cell is initiated by the production of a single-stranded proinsulin molecule. The conversion of proinsulin to insulin involves cleavage and removal of a connecting fragment (C-peptide) from the single-stranded proinsulin molecule with the production of a double-stranded molecule of insulin. The immunological properties of proinsulin are similar to those

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TABLE 7.—*Change with Obesity of Stimuli Which Enchance Insulin Secretion*

Stimuli for Insulin Secretion	*Changes in Obesity*
1. Metabolites	
Glucose	Normal or increased
FFA	Increased
Ketones	Normal
L-leucine	Increased
Ca	Normal
2. Gut Factors	?
3. Neural Factors	
Sympathetic	?
Parasympathetic	?
4. Hormones	
Glucagon	Decreased
Growth Hormone	Decreased
Cortisol	Normal or slightly decreased
Thyroxine	Normal

of native insulin, while the biological activity of the promolecule is only 1 to 2 percent of that of native insulin.[32]

This disparity between biological and immunochemical activities of insulin and proinsulin could provide an explanation for the hyperinsulinemia of obesity. This possibility has been tested, and proinsulin has been found to comprise a similar fraction of total circulating insulin in lean and in obese subjects. (See Chart 2.) The percentage of proinsulin is shown by the solid bars and the glucose and insulin in the upper panels of each pair. Glucose tolerance tests for three lean persons are shown in the upper three pairs of panels of the chart and for three obese persons in the lower three pairs of panels. Although the rise in total insulin is greater in several of the obese subjects, there is little or no difference in the fraction of proinsulin which is produced during glucose stimulation of the pancreatic beta cell.[149]

A decreased rate of insulin turnover could also explain the higher levels of basal insulin. At present, few data are available on the turnover of insulin in obesity. Insulin degradation has been examined in experimental animals, however, and is not altered either *in vivo* or *in vitro*. That is, the removal of insulin is related to the circulating concentration of this hormone.[150] As the concentration of insulin in the circulation rises, the quantity removed also rises because turnover rate remains constant. For a reduction in peripheral degradation to produce a rise in circulating levels of insulin would require that secretion rate remained normal and did not fall with a decline in peripheral turnover. The evidence, although scanty, would suggest that a significant reduction in the clearance of insulin is not the underlying mechanism for the rise in concentration of the fasting insulin in obese subjects.[135]

If the increased basal levels of insulin reflect enhanced secretion of insulin, then the question becomes: By what mechanism is the secretion of insulin augmented? Currently available data indicate that insulin secretion is controlled by a number of humoral and neural signals. These have been reviewed in detail previously. Since the increased basal level in insulin is the predominant effect of obesity, Table 7 has been constructed to compare the concentrations of various humoral and neural signals in the basal state and the response of these stimuli during the infusion. The concentration of glucose, a prime stimulus for insulin secretion, is either normal or modestly increased in obesity. L-arginine, glucagon, growth hormone and calcium, all of which can stimulate insulin secretion, are normal or reduced in obesity.[27,30,31,135,151] Only L-leucine, among secretogogues for insulin, is increased in concentration in the circulation of corpulent people. The elevated levels of this amino acid in plasma led Felig et al[152] to suggest that this amino acid may play an important role in the high levels of insulin found in obesity.

The role of neural signals in the control of insulin levels in obesity is as yet unexplored. However, recent evidence indicates that α-receptor blockage with phentolamine will enhance basal insulin levels in normal subjects while β-receptor blockade will lower it.[83,153] From this summary, it is evident that at present only the increased level of L-leucine provides an explanation for the hyperinsulinemia of the obese state. As will be noted later, however, increased body weight induced in normal persons by a period of enforced overeating also raises the concentration of L-leucine, which suggests that the rise in the concentration of this amino acid is a consequence of obesity rather than a primary cause of the hyperinsulinemia.[154] If this is so, then no satisfactory explanation exists for the hyperinsulinemia of obesity.

Insulin Resistance. Obese persons have normal concentrations of glucose in the presence of high levels of circulating insulin, suggesting resistance to the peripheral actions of insulin. The studies of Rabinowitz and Zierler,[132] using a technique for perfusing the human forearm, were among the earliest studies to suggest resistance to insulin. With their technique, blood specimens from the brachial artery and from superficial and deep venous channels could be collected simultaneously. The deep venous channels drained primarily muscle and the superficial veins drained mainly the fat depots. In their study, the obese subjects were approximately 20 percent above normal weight. This degree of excess weight, however, represents nearly a doubling of the total body fat. Before insulin was given, the uptake of glucose by muscles in the forearm was similar in lean and obese subjects. During a 26-minute intra-arterial infusion of insulin, however, the obese subjects showed smaller effects on the metabolism of glucose than did the lean subjects. From their studies, Rabinowitz and Zierler concluded that both muscle and adipose tissue of obese subjects were resistant to the actions of insulin.[132]

Salans, Knittle and Hirsch[155] used a second approach to examine insulin resistance in obesity. Their technique consisted of incubating an aspirated biopsy specimen of adipose tissue *in vitro* before and after weight loss. The conversion of radioactivity from glucose-1-^{14}C to $^{14}CO_2$ in the presence or absence of insulin was used to measure the effects of this hormone. The difference between insulin-stimulated and basal levels of glucose oxidation was greater after weight loss than before. The difference was due largely to a decline in the basal oxidation of glucose to CO_2 Maximal glucose oxidation in the presence of insulin showed little change with weight loss.

These investigators interpreted their data as indicating that small adipocytes were more sensitive to insulin. An equally valid interpretation would suggest that glucose metabolism without hormones was enhanced by the smaller adipocytes obtained after weight loss, but that the effects of insulin were not changed. Whichever interpretation one takes, the possibility that enlarged adipocytes were the mechanism for resistance to insulin has stimulated numerous studies to examine this hypothesis. Among the factors that have been shown to control the responsiveness to insulin in adipose tissue are (1) the size of the adipocytes,[156] (2) the total caloric intake,[157] (3) the fraction of carbohydrate in the diet before testing the effects of insulin[37,154] and (4) the presence of functional beta cells.[158]

Adipose tissue of growing animals is more sensitive to the effects of insulin than adipose tissue of adult animals.[156,159] However, large adipocytes from older animals can be made as sensitive as small adipocytes from young animals if the old animals are first fasted and then allowed to reaccumulate fat rapidly.[156,159] Thus, enlargement of adipocytes does not necessarily increase their resistance to insulin. A similar conclusion was reached in studies with adipose cells from obese humans.[157] The sensitivity of isolated adipocytes to insulin could be enhanced by overfeeding with a high carbohydrate diet containing 5,000 calories for a period of two weeks. Similarly, brief periods of caloric restriction to 900 calories a day abolished the responses to insulin, indicating critical importance of knowing the total caloric intake before assessing the effects of this hormone.[157]

The composition of the diet is another factor modulating the sensitivity to insulin. There is now convincing evidence that the magnitude of the response of this hormone in small and large adipocytes is a function of the carbohydrate intake.[37,154] The stimulation of glucose oxidation by insulin *in vitro* is enhanced in adipose tissue obtained from rats fed a high carbohydrate diet. A similar effect occurs in human fat. When adipose tissue is obtained from lean human subjects on a high carbohydrate diet and incubated with insulin, more glucose is oxidized to CO_2 than with fat from the same subjects after feeding a low carbohydrate diet.[154]

Intact pancreatic beta cells are a fourth factor involved in regulating the resistance to insulin. Resistance to the hypoglycemic effects of exogenous insulin is a hallmark of the genetically obese mouse (ob/ob).[19] Destruction of the pancreatic beta cells in these animals by injecting alloxan, restores the hypoglycemic effect of exogenous insulin. This occurs without a change in body weight and without a change in size of the adipocytes. These studies indicate that some factor from the pancreas, either endogenous insulin or some other factor, is an essential element in the insulin resistance of these mice.[158]

Although the size of the adipocyte is one factor in determining the resistance to insulin, it appears that total intake of carbohydrates or calories or both, is at least as important. It seems unlikely that resistance of the adipocyte to the action of insulin can provide the entire explanation for impaired effectiveness of this hormone in obese subjects, since the quantity of glucose metabolized by adipose tissue accounts for only a small fraction of total glucose metabolism. Pronounced changes in resistance of adipose tissue alone could not explain alterations in the resistance to the metabolism of glucose. In addition, the studies of Rabinowitz and Zierler[132] in obese subjects indicate that

TABLE 8.—*Some Conclusions from the Vermont Study of Experimental Obesity in Man*

Parameters	*Responses*
Weight Gain	Difficult
Weight Loss	Easy—Returned to Normal
Insulin	
Basal	↑
After Glucose	↑
Oral Glucose Tolerance	Impaired
Intravenous Glucose Tolerance	Impaired
Cholesterol	↑
Triglycerides	↑
Free Fatty Acids	↓ or Unchanged
Cortisol	
Concentration	↓
Secretory Rate	↑
Growth Hormone Secretion	↓
Adipose Tissue	
Cell Size	↑
Number of Cells	Unchanged
Response to Insulin *in vitro*	↓
Lipogenesis (^{14}pyruvate–^{14}C→FA)	↓
Lipolysis	↑
Forearm	
Effect of Insulin	↓
Serum Leucine, Valine	↑

muscle is also resistant to the action of insulin.

The experiments of Sims and his colleagues at the University of Vermont[154] have provided a number of additional insights into the role of diet, adipose tissue and muscle metabolism in the development of insulin resistance in experimental obesity (Table 8). These investigators asked the following question: What happens to the endocrine profile of obesity when lean subjects gain weight by a period of self-induced overeating? For their studies, four groups from the Vermont Penal Institution and one group at the Clinical Research Center volunteered to overeat and gain between 15 and 20 percent of the initial body weight. All subjects in these studies were lean and none had been previously overweight, nor did they have a family history of diabetes. The initial studies were performed while the volunteers ate a diet calculated to maintain body weight. This was followed by several months of increased food intake. Body composition was calculated initially and at the end of the studies. Following the accretion of weight, the subjects submitted to the same tests that they had undergone at the beginning of the study.

The results of these studies are summarized in Table 11 under a number of headings. For the present purpose, we will examine the contribution from the study of insulin level and adipose tissue. After weight gain, regardless of the type of diet used to increase body weight, the basal levels of insulin were increased as was the rise following the administration of glucose. Thus, hyperinsulinemia can be induced in normal subjects by weight gain produced by overeating. Hence, at least some components of the increase in basal insulin in obesity is a consequence of the enhanced weight of these subjects. This concept is consistent with the studies of insulin levels during weight loss when insulin returns toward normal.[137]

The studies of adipose tissue were performed in two different studies. The first utilized aspiration biopsy material before and after weight gain when the volunteers were eating a mixed diet. The second used specimens of fat obtained surgically before and then after weight gain when the volunteers were eating a controlled diet with varying carbohydrate level. In this latter study, one diet contained 300 grams and the other 100 grams of carbohydrate per square meter of body surface. With this experimental design, it was possible to examine the effects of dietary carbohydrate and the size of fat cells on the response to insulin. The utilization of glucose by adipose tissue in the absence of insulin was significantly increased in the enlarged adipocytes. This is the mirror image of observations on weight loss, where basal level of glucose utilization declined as adipocyte cells decreased in size. After a period of weight gain, the increment in radioactivity converted from glucose-1-^{14}C to $^{14}CO_2$ in response to insulin was diminished. The response of adipose tissue to insulin was enhanced on the high carbohydrate diet. Resistance to the action of insulin was also demonstrated in studies on using the perfused forearm. After weight gain, the intra-arterial infusion of insulin showed a pattern similar to that observed by Rabinowitz and Zierler[154] in their studies of people with spontaneous obesity. From these studies, Sims concluded that obesity induced experimentally in human subjects mimics in several respects the changes observed in spontaneous obesity. These respects are (1) an increased level of basal insulin and increased insulin secretion following glucose stimulation, (2) impaired glucose tolerance, (3) insulin resistance as measured by glucose oxidation in adipocytes obtained by either of two experimental approaches, and (4) insulin resistance in muscle similar to that observed in spontaneous obesity.

As was pointed out earlier, diabetes is probably a heterogeneous collection of entities. Obesity is one factor which can bring out a genetic tendency toward diabetes. Obese patients show hyperplasia of the islets of Langerhans in the pancreas[126] and increased insulin secretion. Abnormalities in glucose tolerance are frequently observed in obese patients. The degree of abnormality appears to correlate better with the duration than with the magnitude of the obesity.[127] A person who has been overweight for a long period is more likely to have an abnormality in glucose tolerance than a person of the same weight who gained the weight rather acutely.

This suggests that exhaustion of the insulin secreting capacity occurs gradually, leading to diabetes mellitus. Just as diabetes can develop in obese patients with a long-standing problem, so there is convincing evidence that weight loss will lead to an improvement in glucose tolerance.[128] If, as appears to be the case, obesity increases the demand for insulin, then weight loss would be expected to diminish the demand for insulin and allow the pancreas to recuperate.

Lipid Metabolism, the Polyol Pathway and Vascular Complications

ROBERT H. FISER, MD*

MUCH IS KNOWN about carbohydrate metabolism and the metabolism of fat and protein, yet it is probable that a fuller understanding of the pathophysiology of diabetes and obesity will require a more thorough understanding in each of these fields and their interrelationships. In this discussion I will attempt to relate the known derangements in the metabolism of lipids and lipoproteins to abnormalities of the polyol pathway and how these interrelationships might affect the vascular complications of diabetes.

Lipid Physiology

A brief review of lipid physiology is in order. For a more detailed discussion of lipid metabolism and the transport of lipoprotein, the reader is referred to several recent review articles.[160-163]

Blood lipids—cholesterol, phospholipid and triglyceride—circulate in plasma bound to proteins. Proteins impart solubility to the otherwise insoluble lipid. Fat is transported in plasma as lipid-protein complexes or lipoproteins. Fatty acids circulate in plasma combined with albumin, with a slight amount transported within each of the lipoprotein classes.

Lipoproteins are complex macromolecules composed of varying proportions of lipid, carbohydrates and protein.[160-162] They can be most simply visualized as an inner core of lipid surrounded by a coating of phospholipid and protein. Binding of the lipid to the protein is weak enough to allow ready exchange of lipid among serum lipoproteins and tissue, yet strong enough to allow for separation by several physical and chemical techniques.[161]

Four lipoprotein classes are normally present in plasma. The characteristics of each group are shown in Table 9.[160] Methods for differentiation of these lipoproteins are based on either electrophoresis or ultracentrifugation. Lipoproteins have been separated into chylomicrons, very low density lipoproteins (VLDL or pre-beta), low density lipoprotein (LDL or beta) and high density lipoproteins (HDL or alpha). In brief, chylomicrons are the largest and lightest of the lipoproteins and remain at the origin after electrophoresis. Chylomicrons contain approximately 90 percent lipid and 2 percent protein, the lipid portion consisting mainly of tryglyceride, all of dietary or exogenous origin, with only small amounts of cholesterol and phospholipid. Chylomicrons are synthesized in the intestine cell wall and serve to transport dietary fat from the intestines to the peripheral tissues for utilization. Chylomicrons impart turbidity to plasma, and if the plasma is allow to stand they float to the top or form a creamy layer.

Very low density lipoproteins are the next smallest and lightest. VLDL contain 88 to 95 percent lipid and 5 to 12 percent protein. Fifty percent of the lipid portion is triglyceride. These lipoproteins remain uniformly distributed throughout the specimen after storage in the cold. VLDL transport triglycerides, primarily of hepatic or endogenous origin, that are synthesized from various precursors of free fatty acids and carbohydrate. In the absence of chylomicrons or during the fasting state this lipoprotein class correlates closely with triglyceride levels in plasma.[164]

Low density lipoprotein contains by weight approximately 50 percent cholesterol, 20 percent phospholipid, 10 percent triglyceride and 20 percent protein. Although the precise origin is unknown and mechanisms for disposal are unclear, LDL appears to be derived from the intravascular breakdown of very low density lipoproteins (VLDL).[164] These lipoproteins do not produce turbidity in plasma and are the class primarily responsible for cholesterol transport.

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High density lipoproteins are the fourth and smallest of the lipoprotein classes. They contain 40 to 50 percent protein, 30 percent phospholipid and 20 percent cholesterol. They carry very little triglyceride and do not produce turbidity when present in increased amounts. Their function is also unclear. It should be noted that as each lipoprotein class increases in density, the proportion of protein is greater and of triglyceride smaller.

Hyperlipoproteinemic States

In characterization of the different hyperlipoproteinemic states the classification of Frederickson et al, as modified by the WHO,[165] is useful and is depicted in Table 10. Type I is characterized by increased levels of chylomicrons due to exogenous fat intake. In these cases, lipoprotein lipase, the enzyme that normally hydrolyzes these fat particles, is deficient, leading to decreased removal of chylomicrons from plasma. Triglycerides are increased slightly more than cholesterol. The plasma often appears creamy. This rare defect is found in approximately 1 percent of diabetics.

Type II-A hyperlipoproteinemia is associated with increased levels of LDL or beta lipoproteins. This is often referred to as familial hypercholesterolemia or hyperbetalipoproteinemia. Triglyceride levels are normal while cholesterol levels are greatly increased. Type II-B is characterized by increased levels of both LDL and VLDL lipoprotein with a slight increase in triglycerides. The appearance of the plasma is clear in both states. Both these hypercholesterolemic states are common in the pediatric age ranges.[166]

Type III hyperlipoproteinemia is characterized by an increase in the floating beta band. The VLDL and LDL are probably of abnormal composition. This abnormality is present in a small proportion of diabetics.

Type IV hyperlipoproteinemia is characterized by an increase in VLDL lipoprotein with normal or increased levels of cholesterol. It is particularly common in obesity and in persons with maturity onset diabetes.

Type V is characterized by an increase in VLDL lipoprotein with increases in cholesterol and chylomicrons also present.

Lipoproteinemic Pattern

Large screen studies[167] suggest that the incidence of diabetes within Type I and II subgroups is the same as in the general population. How-

TABLE 9.—*Human Plasma Lipoproteins*

		Fraction		
	Chylomicrons	*Very Low Density*	*Low Density*	*High Density*
Density	<1.006	1.006	1.006–1.063	1.063–1.21
Sf	>400	20–400	0–20	
Diameter, A°	5,000–10,000	300–700	200–250	100–150
Electrophoretic mobility	origin or α_2	Pre-β (α_2)	β	α_1
*Plasma (mg per 100 ml)	100–250	50–200	200–400	150–400
Appropriate percentage composition				
Protein	2	9	21	33
Phospholipid	7	18	22	29
Cholesterol				
Free	2	7	8	7
Ester	6	15	38	23
Triglyceride	83	50	10	8

*Obtained 10 to 14 hours after last meal.

TABLE 10.—*Classification of Hyperlipoproteinemia*

		Lipoprotein				*Lipids*		
Type	*Chylomicrons*	LDL β	VLDL *pre-β*	*Floating β*	*Appearance of Standing Plasma*	*Cholesterol*	*Triglyceride*	*Ratio Chol: Triglycerides*
I	+	..	..	..	Creamy	↑	↑ ↑	<0.2
II-A	..	+	..	..	Clear	↑ ↑	N	>1.5
II-B	..	+	+	..	Clear or Faintly Turbid	↑	↑	Variable
III	..	..	..	+	Turbid	↑	↑	Freq. >1.0
IV	..	..	+	..	Clear or Turbid	N or ↑	↑	Variable
V	..	..	+	..	Creamy	↑	↑ ↑	>.15; <.06

TABLE 11.—*Maternal Complications of Diabetes Mellitus During Pregnancy**

Complication	*No. of Patients*	*No. with Complication*	*Percent*
Mortality	4,850	39	0.8
Toxemia	3,698	889	24.0
Hydramnios	2,937	604	20.5
Acidosis	1,871	193	10.3

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*From Spellacy WN: Diabetes mellitus complicating pregnancy, Modern Med 37:91, 1969.

TABLE 12.—*Fetal and Newborn Mortality in Pregnancies Complicated by Diabetes Mellitus**

Timing of Death	*No. of Patients or Infants*	*No. With*	*Percent*
Abortions	2,521	198	7.9
Fetal death	3,347	382	11.4
Neonatal death	3,300	280	8.5
Total perinatal deaths	4,374	868	19.8

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*From Spellacy, Modern Med. 37:91, 1969.

ever, patients characterized as having Types III, IV and V have a much higher incidence of diabetes and obesity than the normal population. A greater than 50 percent occurrence of some degree of glucose intolerance is noted with Type III, and an even higher incidence with Type IV and V. It is believed by some observers that if a patient is an insulin-dependent diabetic, diabetes probably occurs first, with the hyperlipidemia second. On the other hand, the majority of patients who have maturity onset diabetes are obese and do not require insulin for regulation.[168] Indeed, they may have high levels of insulin. In these patients, it is felt that diabetes, obesity and hyperlipidemia may be expressions of the same metabolic aberrations, but which of these conditions is primary and which secondary is not known at present.

What, then, are the pathophysiologic mechanisms important in regulating these defects? The most important regulator of lipoprotein concentration in plasma is demand of the tissues for fuel. This is derived primarily from the transport of triglycerides in the VLDL fraction through plasma. Assuming constant pool sizes and steady state conditions, the concentration of VLDL at any time reflects a balance between secretion or production from the liver and utilization or removal by the peripheral tissues. Hyperlipidemia, assuming pool sizes remain constant, can most simply result from either increased production, decreased utilization or both. Evidence for each of these states in diabetic persons is available, but far from clear-cut.

Gross and Carlson[169] have presented evidence of increased secretion of triglycerides by the liver following the onset of acute diabetes induced by anti-insulin serum and a reduction in triglyceride levels by decreasing free fatty acid levels with nicotinic acid. In contrast, no increase in hepatic triglyceride output was noted in chronically diabetic dogs[170] or rats.[171] Porte[172] was unable to demonstrate any effect on triglyceride levels in plasma after lowering free fatty acid levels by 70 percent with nicotinic acid in a patient with ketoacidosis. Bagdade et al[173] showed that acute insulin withdrawal in insulin-dependent diabetics results in a fall in post-heparin lipolytic activity, thereby leading to decreased removal.

The degree of obesity is clearly related to the hyperlipidemia of diabetes. It is difficult to separate factors affecting maturity onset diabetes from those related to obesity. In many instances both are characterized by hyperinsulinism and a state of insulin resistance.[168] High insulin is thought to promote hepatic triglyceride synthesis. Insulin levels can be increased by a variety of antagonists —corticosteroids, growth hormone, catecholamine, estrogens and free fatty acids (FFA) and possibly other unknown factors. Resistance to peripheral uptake of glucose in patients with latent diabetes has been best documented by Shen et al, who utilized continuous infusions of glucose, propranolol, epinephrine and insulin to document peripheral glucose intolerance.[174] They used the term *impedance* to account for the tissue insensitivity to insulin-mediated glucose uptake, this insensitivity presumably leading to increased insulin levels and thus increasing VLDL production.

Triglyceride FFA as well as FFA bound to albumin may also increase insulin levels by directly stimulating the pancreas[175] and leading to antagonism at the periphery. Randle has often proposed FFA as being important in the pathogenesis of diabetes.[176]

It seems likely that one or both mechanisms—that is, disturbances of production or removal—may be present in diabetes. These disturbances would vary considerably according to free fatty acid and insulin levels and turnover times. It is evident that further dynamic studies formulating turnovers and secretion rates of free fatty acids and triglycerides as well as lipoprotein lipase levels at various tissue sites are necessary before a full understanding of this defect in lipoprotein metabolism can be reached.

Accordingly, no clear-cut evidence is available to explain the elevated lipids in man. Although not all patients with diabetes have elevation of serum lipids, patients with (1) pancreatitis,[177] (2) ketoacidosis,[178] (3) inadequate insulin treatment,[179] and (4) endogenous hyperlipoproteinemia[180] all have increased blood lipids with resultant accelerated risk of coronary artery and large vessel vascular disease. The mechanism by which these elevated lipids lead to vascular complication may be related in part to the recently described polyol pathway of glucose metabolism.

Polyol Pathway

The polyol pathway has been implicated in a number of the delayed complications of diabetes.[181] A recent and thorough review of the pathological significance of this pathway has been published.[182] Polyols are organic compounds that contain three or more hydroxyl groups. They are commonly used to designate the reduction product of a sugar. Glucose is reduced to its polyol (sorbitol) by aldose reductase, an enzyme which is present in a wide variety of tissues throughout the body.[183] The sorbitol which accumulates is oxidized to fructose by sorbitol dehydrogenase. Neither enzyme is affected by insulin.

Normally these non-insulin dependent enzymes account for only a small fraction of the total glucose utilized in the body. The major pathway for glucose entering the cell is phosphorylation at the 6-position by hexokinase. The resulting glucose 6-phosphate enters one of several pathways. At normal physiologic concentrations of glucose, the polyol pathway accounts for approximately 1 percent of total glucose utilization. With hyperglycemia, more glucose is metabolized to sorbitol which accumulates in tissues because of its slow oxidation to fructose. Accumulation of sorbitol within the tissues increases the osmotic pressure and is associated with an increased water content, leading to edema. This edema has been associated with abnormalities in the concentrations of electrolytes, amino acids and myoinositol in tissues.[182] The polyol pathway, although studied most thoroughly in the lens of the eye where it is thought to produce cataracts,[184] the brain (cerebral edema)[185] and possibly a contributing factor in neuropathies[186] also has been shown to be present in the aortic wall.[187] The activity of this pathway appears to be regulated in part by concentrations of the glucose and possibly by hormonal controls. Sorbitol levels in rabbit thoracic aorta can be altered by the *in vitro* addition of a number of hormonal and pharmacological agents. Epinephrine, isoproterenol, dibutyryl-3′, 5′-adenosine monophosphate, ouabain and angiotensin II all lead to increased concentration of sorbitol.[182]

Whether these compounds have similar effects in man has not been determined. Nonetheless, increased concentrations of sorbitol lead to edema with changes in the content of electrolyte and amino acids and can decrease oxygen consumption by producing hypoxia. A reduction of oxygen within the aorta might contribute to the development of atherosclerosis by modifying the metabolism of cholesterol and triglyceride within the tissues. Increased lipid level in a diabetic patient could lead to an accumulation of these lipids in large vessels.[182] The polyol pathway may thus be a link between hyperglycemia, abnormalities in lipid metabolism and changes in large vessels.

Atypical Diabetic Coma

RONALD S. SWERDLOFF, MD*

COMA IS NOT a rare concomitant of diabetes mellitus. The causes of coma in diabetic patients are many and deserve considerable thought and attention. While ketoacidosis is the traditional cause of severe obtundation in diabetic patients, it must be carefully distinguished from other causes such as hypoglycemia, nonketotic hyperosmolar coma, lactic acidosis, and of course any other cause of metabolic dysfunction. Additional problems in diagnosis and treatment arise when several of these pathogenic mechanisms exist in a single comatose patient.

The subject of ketoacidosis will not be discussed in this symposium. (Recent reviews of ketoacidosis include those of Beigelman,[188] Bortz et al[189] and Assan et al.[190] Instead, attention will be directed toward the hypoglycemic, hyperosmolar and lactic acidosic forms of coma.

Hypoglycemia in Diabetic Patients

Table 13 lists some of the causes of hypoglycemia in diabetic patients. Clearly, insulin overdosage must be considered as the most likely cause of obtundation in the insulin-treated diabetic. The causes of insulin overdosage include: overpre-

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TABLE 13.—*Hypoglycemia in the Diabetic*

A. Insulin Overdose
  1. Overprescribing
  2. Wrong insulin taken
  3. Incorrect measuring—poor vision
  4. New site—less fibrosis
  5. Failure to eat
  6. Increased exercise
  7. Recovery from resistant state (e.g., infection)
  8. Variability in insulin requirement
B. Sulfonylureas
C. Biguanides—unusual
D. Drug interactions
E. Superimposition of another cause of hypoglycemia, e.g., hypopituitarism, adrenal insufficiency, malignancy
F. Postprandial hypoglycemia of mild adult onset diabetes mellitus (transient)

TABLE 14.—*Drug-Induced Hypoglycemia as the Result of the Combination of a Hypoglycemic Drug Plus a Potentiating Drug (Modified from Seltzer[192])*

A. Sulfonylurea plus
  1. Sulfa containing antimicrobials
  2. Bishydroxycoumarin
  3. Phenylbutazone
B. Insulin Plus
  1. Propranolol
  2. Oxytetracycline
  3. EDTA
  4. Mefanazine
  5. Manganese

scribing by the physician; incorrect insulin dosage taken (U 80 instead of U 40); incorrect measuring of insulin, sometimes due to poor vision; a new location for administration of insulin (an area with less fibrosis); change in dietary regimen; increased exercise; recovery from a resistant state such as infection without modification of the insulin dosage; addition of a drug that has either an independent hypoglycemia action or the capability of augmenting the effect of insulin; and variability of insulin requirements, often for unexplained reasons.

The sulfonylurea drugs are important causes of hypoglycemia in adult onset diabetes and may result in profound hypoglycemia, particularly in elderly patients. Chlorpropamide may represent a particularly vexing problem because of the prolonged duration of hypoglycemia which is often produced.

The metabolic pathways of the individual sulfonylurea agents are important considerations in the prescribing of these drugs. Tolbutamide and acetohexamide are metabolized by the liver; with hepatic dysfunction, higher serum drug levels than normal may be present. In addition, the metabolic products of acetohexamide are themselves potent hypoglycemic compounds which are excreted in the urine. Thus, both hepatic and renal dysfunction may result in an extremely high serum level of active material during treatment with acetohexamide and may result in severe and prolonged hypoglycemia. Two other drugs, chlorpropamide (which is excreted by the kidney relatively unchanged) and tolazamide, may produce severe hypoglycemia when administered to patients with renal disease.

Although biguanides are an unusual cause of hypoglycemia, extremely large doses, such as taken in attempts at suicide, may produce severe and fatal lowering of blood sugar.[191]

Drug interactions are also important considerations in the production of hypoglycemia. This subject has been reviewed in detail by Seltzer.[192] These drug interactions can be divided into two categories: (1) the combination of two drugs with intrinsic hypoglycemia action, such as alcohol or salicylate when administered to insulin or sulfonylurea-treated patients or by the combination of various types of antidiabetic drugs (for example insulin plus sulfonylureas); (2) the addition of a drug without intrinsic hypoglycemic action but which potentiates the effects of a hypoglycemic drug. Examples are listed in Table 14.

A particularly difficult problem is that of alcohol consumption in diabetic patients. The restricted caloric intake associated with alcohol ingestion may produce a severe and sometimes fatal form of hypoglycemia in a diabetic patient. This point has been emphasized by Arky,[193] who described extremely high mortality rates in diabetic patients with alcohol-induced hypoglycemia.

The late postprandial hypoglycemia of the mild adult-onset diabetic, while often aggravating in terms of symptoms, does not produce sufficient duration of hypoglycemia to result in significant cerebral obtundation.

The important points about treatment of the hypoglycemic patient, are (1) the need for prompt recognition of the cause of obtundation and (2) the need for prompt and sufficiently prolonged administration of glucose to assure persistent correction of the lowered glucose levels. As a general rule, every unconscious patient should be considered to be hypoglycemic until proven otherwise; a blood specimen should be obtained immediately and tested with dextro-sticks before being sent to the laboratory. This will allow detection of low blood sugar within minutes after the patient reaches the hospital. Treatment with 50 milliliters of 50 percent glucose solution given intravenously will immediately awaken more than 80 percent of all hypoglycemic patients. Failure to arouse a patient may well represent evidence of more severe brain damage. The bolus of 50 percent glucose solution should then be followed by a continuous infusion of 10 percent glucose at a rate needed to maintain the blood sugar at approximately 100 mg per 100 ml. The major error made in treatment of such patients is to discontinue the glucose therapy too early without monitoring subsequent blood sugar levels carefully. The effects of a drug such as chlorpropamide may persist for days. Even when blood sugar concentrations seem to be maintained well on a very slow drip of 10 percent glucose solution, it is recommended that the patient be maintained on intravenous 5 percent glucose solution until it is demonstrated that hyperglycemic or normoglycemic levels are maintained at a very slow rate of infusion.

Parenteral glucagon is an ineffective treatment in a large percentage of hypoglycemic obtunded patients.[194] The use of glucagon in the treatment of hypoglycemic coma should therefore be reserved for situations in which intravenous glucose is not available.

Hyperosmolar Nonketotic Hyperglycemia Coma

Hyperosmolar nonketotic coma, the second most common form of hyperglycemic diabetic comas, is characterized by severe hyperglycemia, hyperosmolarity, volume depletion and obtundation in the absence of severe ketosis. While criteria for ketosis are somewhat arbitrary, Duncan[195] and Arieff and Carroll[196] have used the following definition in their analysis of comatose nonketotic diabetic patients: Ketosis is present when serum diluted 1:1 with water gives greater than 2+ acetest response. This corresponds to approximately 40 to 50 mg per 100 ml of acetone plus acetoacetic acid in the serum. Concentrations of serum ketones greater than this produce significant acidosis and will be classified in the more traditional ketoacidotic group.

There have been a number of reviews of nonketotic hyperosmolar coma in the past several years.[196-198] Evaluation of clinical characteristics of patients with this disorder reveals no sex predominance, with a typical patient being a middle aged or elderly adult-onset or previously undiagnosed diabetic. A few patients have been insulin-dependent and several have had previous episodes of diabetic ketoacidosis.

The patients are often misdiagnosed as having acute strokes or seizure disorders or are admitted for associated problems including pancreatitis, gastroenteritis and infection. The events which precede the admission for coma include polyuria, polydipsia and increasing lethargy, which ultimately result in unresponsiveness. The duration of illness before admission to hospital is often relatively long, with three to seven days of polydipsia being common and two to three weeks of symptoms not rare.[196] Infection commonly preceded hospital admission and in many instances was the precipitating event. Other underlying conditions and precipitating events include chronic renal disease,[196,197] hypertension,[196,197] congestive heart failure,[196,197] gastrointestinal bleeding,[197] protracted diarrhea,[196-199] pancreatitis,[196,197,200,201] hypothermia,[202] severe burns[203] and fluid deprivation.[189]

A number of drugs have been implicated in the pathogenesis of nonketotic hyperosmolar coma. They include diphenylhydantoin (Dilantin®),[197,204] diuretics,[196-198,205] glucocorticoids,[196-198,206] reserpine,[197] and chlorpromazine;[197] each of these drugs has been demonstrated to impair glucose tolerance. In addition, intravenous administration of glucose,[203] infusion of mannitol,[197,207] withdrawal of insulin,[197] and peritoneal hemodialysis[196,208] have also precipitated this metabolic disorder. Particularly distressing is the fact that in at least some of the patients hyperosmolar nonketotic coma develops following admission to the hospital and while treatment for other problems is being carried out.

Mortality rates in this disorder are extremely high when compared with ketoacidosis; approximately half of the patients with hyperosmolar nonketotic coma described in the literature died while in hospital.[196,198] In the largest series available,[196] patients survived in only 14 of 33 episodes. In that series, 11 patients died within two days of the recognition of the hyperosmolar coma without regaining consciousness. These patients were not different from the surviving patients with regard to blood glucose concentrations or plasma osmolality. Six of the 11 patients who died had blood sugar of less than 250 mg per 100 ml before death. Seven of the 11 died of concomitant medical illnesses including Gram-negative pneumonia and Gram-negative sepsis. In the remaining four deaths, the patients differed from the sur-

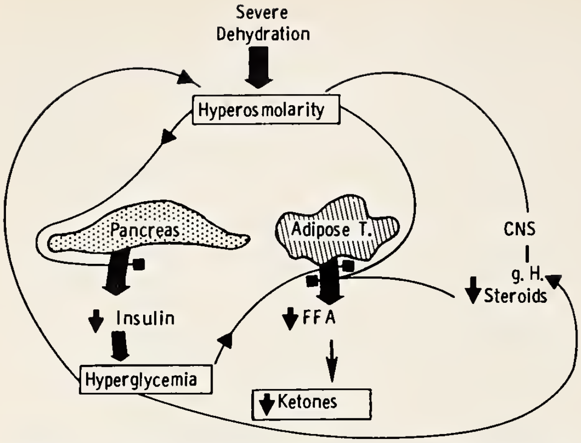

Chart 3.—Proposed pathogenesis of hyperosmolar-nonketotic coma. In this sequence severe dehydration produces hyperosmolarity which in turn: (1) depresses the release of free fatty acids from adipose tissue, (2) inhibits the secretion of insulin, and (3) impairs central nervous system control of growth hormone and cortisol responses. The low level of insulin results in increased hyperglycemia which subsequently aggravates the hyperosmolarity and further inhibits lipolysis.[197]

viving population by the long duration between onset of coma and initiation of therapy. In 22 episodes of nonketotic hyperosmolar coma, the patients regained consciousness after correction of all metabolic abnormalities and adequate restoration of body fluid deficits. Despite this, eight of these 19 patients subsequently died of complicating illnesses.

Acid base balance in patients with hyperosmolar coma in the series of Arieff and Carroll indicated that 12 or the 20 patients evaluated had metabolic acidosis (blood pH being 7.35 or less and serum bicarbonate less than 22 mEq per liter). Measurements of cerebral spinal fluid pH indicated similar levels. Ten of the 15 patients studied had significant elevation of arterial lactate concentration while only two patients had serum lactate levels in the range commonly found in spontaneous lactic acidosis. In the latter two patients, the onset of lactic acidosis was marked by the appearance of hypertension, hyperventilation, and ultimately death.

Blood glucose, insulin, free fatty acid, growth hormone and cortisol levels have been compared in patients with ketoacidotic and nonketotic hyperosmolar coma. Blood glucose and plasma insulin concentrations were similar in the two groups.[197] Free fatty acids were considerably higher in patients with ketoacidosis than in those who were in nonketotic coma.[196,197] Growth hormone values have been reported to be lower in hyperosmolar nonketotic coma in some[197,198,209] but not all series.[196] Serum osmolarity in the two largest series of nonketotic coma approximates 380 milliosmols per liter[196,197] a level which is higher than in most series of ketoacidosis.

The characteristic difference between these patients and those with ketoacidosis is a relatively low level of ketones in the serum. The presence of a lower level of free fatty acids suggests that these patients may differ from those patients with ketoacidosis with regard to lipolysis. The presence of higher levels of growth hormone[197,198,209] and cortisol,[197,209] both lipolytic hormones, in patients with ketoacidosis is a possible pathogenic explanation for the discrepancy between these two diabetic conditions. Another factor which might be considered in the pathogenesis of this syndrome is the possibility that dehydration may result in impaired ketogenesis, probably by impairing free fatty acid release from adipose tissue.[197,210,211]

The suggestion that hyperglycemia *per se* results in inhibition of ketosis in hyperosmolar patients would not be born out by the similar glucose levels in a controlled study of ketoacidosis and hyperosmolar coma.[197] Immunoreactive insulin levels seem to be similar in the two conditions,[197] indicating that higher levels of plasma insulin are not responsible for the lack of ketosis in hyperosmolar coma. (More data would be helpful in validating this point.)

While adrenal cortical steroids have been clearly associated with precipitation of hyperosmolar coma,[196-198,206] hyperglucocorticoidism is not the cause of hyperosmolar nonketotic coma in the majority of patients. This is clearly demonstrated by the data indicating that levels of glucocorticoids are usually lower in hyperosmolar patients than those with ketoacidosis.

We have reviewed above some of the data which compare patients with ketotic and those with nonketotic hyperosmolar diabetic coma. The reason ketosis develops in some patients has been of considerable interest to a number of investigators. Gerich et al[197] postulated the following sequence of events to explain the lack of ketosis (Chart 3): Dehydration, due to either glycosuria, pancreatitis, burns, drugs or inability to obtain fluid, leads to hyperosmolarity. Hyperosmolarity in turn depresses the secretion of pancreatic insulin (inappropriately low for the degree of hyperglycemia), inhibits adipose tissue lipolysis and impairs control of growth hormone and cortisol by the central nervous system. Impaired secretion

TABLE 15.—*Anion Gap in Metabolic Acidosis*

Anion Gap $= Na_S - (Cl + Hco_3) = 12$ mEq/L

Causes:
1. Ketoacidosis
2. Azotemic Renal Disease
3. Lactic Acidosis
4. Drugs and Toxins (salicylates, methyl alcohol, ethylene glycol, paraldehyde)

TABLE 16.—*Classification of Causes of Elevated Blood Lactate Level*

Etiologic Factors	*Range of Lactate Concentration (mEq/L)*
A. Without excess lactate (normal L:P ratio)	
1. Infusion of pyruvate	2.0–4.9
2. Infusion of glucose	Up to 1.7
3. Infusion of $NaHCO_3$	Up to 2.4
4. Glycogen storage disease	3.3–14.4
B. With or without excess lactate (normal or increased L:P ratio)	
1. Hyperventilation	1.87–22
C. With excess lactate (increased L:P ratio)	
1. Exercise	8.0–22
2. Epinephrine	1.3–2.9
3. Cardiovascular insufficiency	
a. Shock	2–35
b. Cardiopulmonary bypass	2–8
4. Acute hypoxemia	3–4
5. Severe anemia	Up to 1.9
6. Leukemia	12.2–25
7. Diabetes mellitus	10.2–30.8
8. Phenformin therapy	10–31
9. Ethanol ingestion	Up to 8
10. Spontaneous (idiopathic)	3.1–23

A distinction is made between those causes which are associated with a normal L:P ratio (no excess lactate) and those associated with an increased L:P ratio (excess lactate) and therefore tissue hypoxia. From Waters et al, Amer. J. Med. 35: 781, 1963 as modified by Oliva.[214]

of insulin results in hyperglycemia, which aggravates the hyperosmolarity and further inhibits lipolysis. Thus, the hyperosmolarity, hyperglycemia, diminished growth hormone and cortisol all contribute to decreased release of free fatty acid from adipose tissue. The resultant low levels of circulating free fatty acids are responsible for the failure to develop ketosis in this syndrome.

A role of cerebral edema as a major cause of death in patients with nonketotic hyperosmolar coma was suggested by animal studies[212] and by its demonstration in patients with ketoacidotic coma.[213] Measurement of cerebrospinal fluid pressures and autopsy examinations of the brain[196] have indicated that cerebral edema is an unusual concomitant of even the most severe cases of hyperosmolar nonketotic coma.

Treatment of patients with hyperosmolar coma must be directed toward (1) identification and correction of an underlying precipitating cause such as infection, or drug administration, (2) correction of the extreme degree of volume depletion, and (3) correction of the hyperosmolar hyperglycemic state. It is generally agreed that massive fluid replacement is required. There is some controversy regarding the form of the initial fluid replacement; the majority of the investigators currently advocate 0.45 percent saline solution unless the patient is in frank shock. The usual deficit is approximately 25 percent of the total body water. Potassium chloride replacement must be begun in the first few hours as soon as the urine output has been demonstrated to be adequate. The initial insulin dosage should be quite modest relative to doses given to patients with ketoacidosis; some patients are quite sensitive to insulin therapy, as they lack the resistance seen with severe metabolic acidosis. Insulin should be given intravenously during the early course of treatment. Under good management the most important factor in preventing mortality is early recognition and treatment of this disorder.

Lactic Acidosis

Lactic acidosis represents a third example of nonketotic coma occurring in diabetic persons.[214] It must be differentiated from other metabolic acidosis such as ketoacidosis, uremia or that produced by drugs and toxins such as salicylates, methyl alcohol, ethylene glycol or paraldehyde (Table 15). In each of these situations an "anion gap" is identified by analysis of the electrolyte concentrations in blood. An appropriate index of suspicion should result in the identification of elevated serum lactate concentrations.* A rule of thumb which can be used to estimate the ketoacid contribution of the anion gap is to assume that 4+ acetest-positive reaction (measures acetoacetic acid) in undiluted serum reflects approximately 6.0 to 7.5 millimols per liter of "total ketones." The same relationship holds for each dilution of serum, thus allowing an estimate of the proportion of the anion gap produced by the ketoacids present. This can later be confirmed by quantitative determination of serum ketoacids and lactate measurements done in the clinical laboratory.

Lactic acidosis occurs under a number of conditions in which serum lactate levels are elevated (Table 16). Lactate is of course a normal meta-

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*Mixed acidosis (lactic and ketotic) may occur; the assessment of the relative influence of each is a valuable asset in planning therapy.

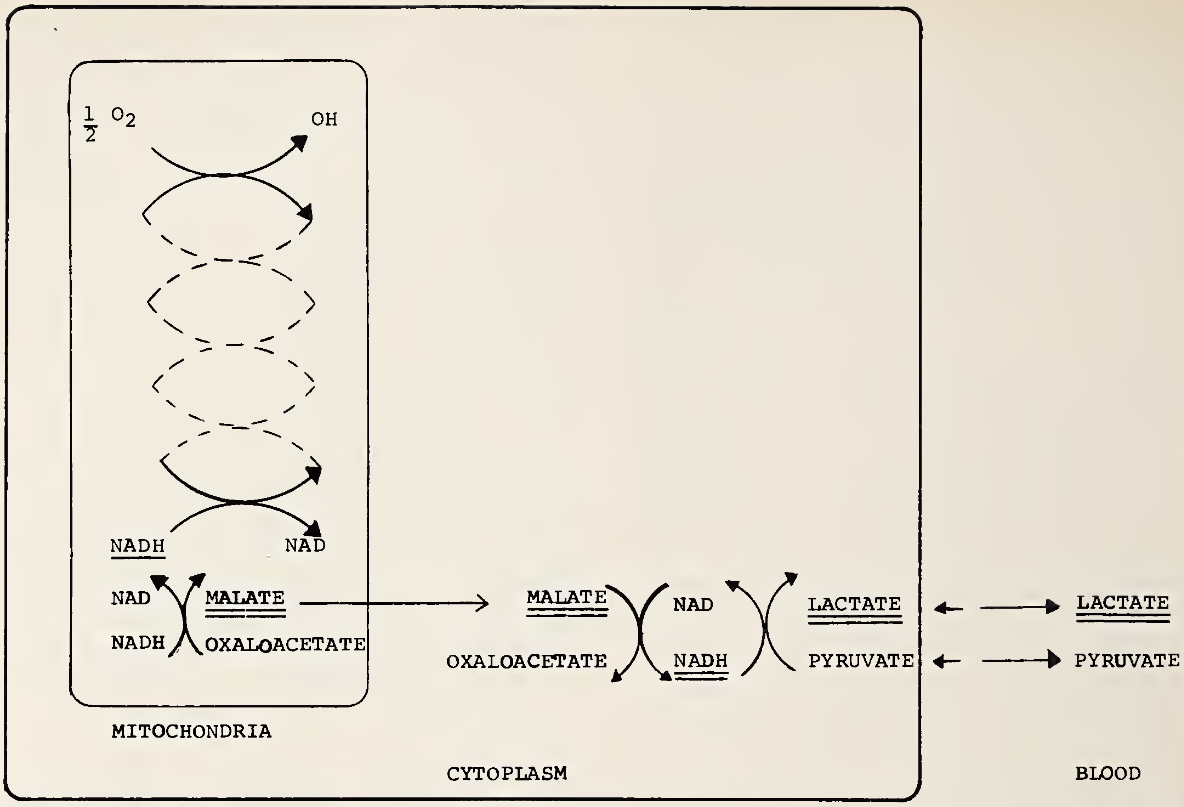
$\frac{1}{2}$ O2
OH
NADH
NAD
NAD
NADH
MALATE
OXALOACETATE
MITOCHONDRIA
MALATE
OXALOACETATE
NAD
NADH
LACTATE
PYRUVATE
LACTATE
PYRUVATE
CYTOPLASM
BLOOD

Chart 4.—Schematic representation of a muscle cell. The quantity of lactate produced is related to the high levels of NADH which cannot adequately be oxidized by the mitochondrial systems. Thus the hydrogens from NADH are transferred to lactate which then leaves the cell along with its hydrogen ion to produce the lactic acidosis.

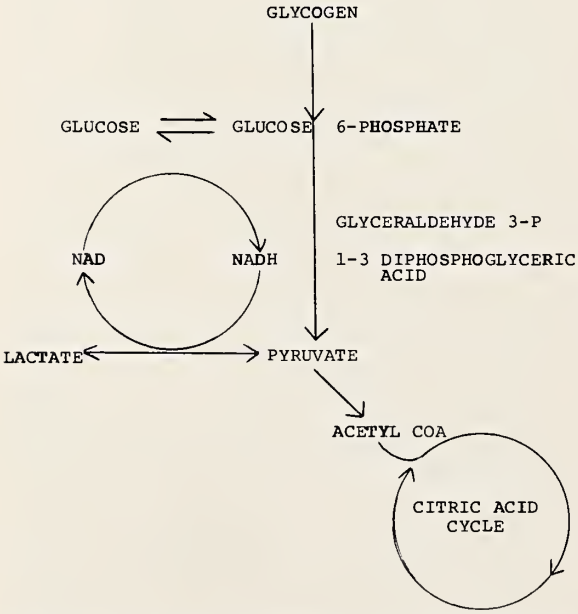
GLYCOGEN
GLUCOSE
GLUCOSE 6-PHOSPHATE
GLYCERALDEHYDE 3-P
1-3 DIPHOSPHOGLYCERIC ACID
NAD
NADH
LACTATE
PYRUVATE
ACETYL COA
CITRIC ACID CYCLE

Chart 5.—Schematic representation of the muscle cell showing the principal source of carbon and hydrogen for the production of lactate.

bolic byproduct of the metabolism of glucose (Chart 4). It is in equilibrium with pyruvate according to the following reaction:

$$\text{Pyruvic Acid} + \text{NADH}_2 \overset{\text{LDH}}{\rightleftarrows} \text{Lactic Acid \& NAD}$$

Lactate can only be metabolized by conversion to pyruvate. Thus either an increase in the concentration of pyruvate or an increase in the NADH_2/NAD ratio will result in increased serum lactate levels. Whenever glycolysis is accelerated, pyruvate and lactate are increased (usually in a ratio of 10 to 1). With tissue hypoxia, however, lactate is produced out of proportion of pyruvate. This occurs as the result of an increased reduction of NAD to NADH_2 in the mitochondria in the face of oxygen deficit. By a series of coupled reactions, the increased NADH_2/NAD ratio in mitochondria results in increased NADH_2/NAD ratio in cytoplasma, forcing the pyruvate:lactate equilibrium to the right (Chart 5).

Tissue hypoxia due to impaired oxygenation of blood, to impaired delivery of oxygenated blood or to tissue metabolism disproportionate to the available oxygen supply (as in severe exercise) will result in increased lactic acid production.[215,219,220]

Patients with diabetes mellitus have an increased disposition toward increased lactic acid levels. This is often due in these patients to significantly increased cardiovascular disease with associated tissue hypoxia or may be due to increased lactic acid production associated with phenformin administration.[214,215,221] Lactic acidosis in the diabetic is often associated with poor control as evidenced by hyperglycemia but may be associated at times with normoglycemia,[216] or even hypoglycemia.[217,218]

Since phenformin is a commonly used drug in the treatment of diabetes, further comment on its potential role in the pathogenesis of lactic acidosis is appropriate. There is little question that phenformin administration results in increased production of lactic acid both in diabetic and in nondiabetic persons.[221-223] This effect appears to be due to inhibition of cellular aerobic metabolism[224] and is dose-related.[214] While increases in levels of serum lactic acid occur commonly in the upper part of the therapeutic dosage range, the production of clinically important lactic acidosis is unusual in the absence of other precipitating events. The majority of the patients described with phenformin-associated lactic acidosis had a history of alcohol excess, were in shock or had other reasons for tissue hypoxia. There are reports of lactic acidosis attributable to phenformin taken in attempts at suicide.[191,221]

Whether or not phenformin in normal dosage may result in clinically significant lactic acidosis in the absence of other causal events, it is likely that it will aggravate lactic acidosis occurring from any other cause. This may be the result of additive effects of phenformin on lactic acid production or, more importantly, its effect on decreased removal of circulating lactic acid.[222] For these reasons, phenformin therapy should be avoided in any patient with evidence of vascular disease.

Treatment of lactic acidosis has in general been disappointing. Emphasis must be placed on (1) early recognition; (2) elimination of the sources of lactate overproduction, such as correction of shock, hypoxemia, tissue hypoxia, anemia and elimination of precipitating drugs; (3) correction of acidosis with bicarbonate therapy, and (4) conversion of lactic acid to pyruvate by the administration of methylene blue.[225]

Diabetes, Pregnancy and Obesity

DELBERT A. FISHER, MD*

IMPORTANT ALTERATIONS in maternal metabolism occur during pregnancy, and it is now generally agreed that these changes are largely mediated by placental hormones. These events have been looked upon, teleologically, as evolutionary changes designed to help guarantee a continuing transplacental supply of energy and growth substrate to the fetus. However, for the mother the net effect of these alterations tends to be catabolic or anti-insulin, with the result that pregnancy is a stress to a diabetic or pre-diabetic person. More specifically, fasting insulin levels and the plasma insulin response to glucose and tolbutamide increase progressively throughout gestation.[226-229]

Since the rate of insulin degradation is enhanced during pregnancy,[230,231] these increased basal and stimulated concentrations of insulin reflect increased insulin secretion. In addition, the tolerance to exogenous insulin is increased[232,233] and fasting plasma levels of FFA are elevated.[234] These changes indicate progressive insulin resistance and, in an insulin-dependent diabetic woman, insulin requirements near term are on the average increased by 60 to 75 percent.[234] This pancreatic stress is sufficient in many genetically predisposed persons to provoke gestational diabetes mellitus. The incidence of gestational and insulin dependent mellitus in pregnancy probably ranges between 1 and 2 percent.[235]

The mechanism of insulin resistance in pregnant women is not entirely clear. It is not attributable to decreased glycogen stores,[236] altered catecholamine metabolism,[237] increased cortisol secretion,[238] or increased secretion of pituitary growth hormone.[239-241] Rather, it appears to be secondary to placental secretion of chorionic somatomammotropin (HCS),[229,239,242] estrogens and progestins.[229,243-245]

HCS has both growth hormone and prolactin-

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like effects and has been shown to impair glucose tolerance in hypophysectomized rats, to inhibit peripheral glucose utilization in normal subjects despite increases in plasma insulin concentrations, and to stimulate FFA release from fat depots.[246,247] There also is evidence that HCS may directly stimulate the function of the pancreatic beta cells.[242,248] The increase in secretion of insulin observed in hypophysectomized rats after administration of HCS, however, does not appear to be mediated through changes in blood sugar.[242] Finally, the progressive increase in maternal levels of HCS during gestation coincides temporally with the increasing concentrations of plasma insulin and progressive augmentation of the insulin response to glucose.[228] Estrogens and progestins also produce insulin resistance[229,243-245] and will precipitate diabetes mellitus in genetically predisposed persons.[244,245] Maternal blood levels of these steroid hormones increase progressively during gestation in a manner generally parallel to the progressive hyperinsulinemia.

The incidence of maternal complications of pregnancy is increased significantly by diabetes mellitus; major among these are toxemia, hydramnios, and acidosis. However, infection, particularly of the urinary tract, proliferative retinopathy, and hypoglycemia, especially early in gestation, also are common. The incidence of major complications has been reviewed recently by Spellacy,[235] who collated data from 29 series of patients reported between 1953 and 1967 (Table 11). Mortality varied from zero to 4.8 percent, toxemia from 3 to 53.7 percent, hydramnios from 3.5 to 51.4 percent and acidosis from zero to 37.2 percent. Fetal mortality also was collated and is summarized in Table 12.[245] Abortions varied from 1.2 to 18 percent, fetal deaths from 1.6 to 38.1 percent, neonatal deaths from 3.3 to 15.5 percent. Total perinatal deaths varied in frequency from 7.9 to 44.8 percent,[245] and the mean value 19.8 percent (Table 12) is several times higher than the accepted control figure of about 3 percent. In addition, the incidence of congenital anomalies is increased from the average rate of about 2 percent to a mean value of 5.8 percent.[245]

In a general way the incidence of fetal anomalies and the increased fetal mortality can be correlated with the severity and duration of maternal diabetes mellitus.[249,250] Thus, Nelson, Gillespie and White[251] have proposed a classification (A through F, plus R) based on maternal age at onset, duration of disease, and presence of demonstrable vascular complications from which fetal risk can be estimated. This risk relates, basically, to the development and extent of placental disease. The pathologic changes observed in the diabetic placenta include subsyncytial edema, syncytial hyperplasia, avascularity of villi, and the deposition of periodic acid shift-positive material in vascular intima.[252,253] There is a high degree of correlation between the extent of these changes, assessed from placental biopsy, and perinatal morbimortality.[252] Thus, as functioning placental tissue is progressively reduced in volume, fetal survival is progressively compromised. For this reason, it is now recommended that diabetic patients have serial tests of placental function; the most commonly employed are measurements of maternal excretion of estriol and maternal blood levels of human chorionic somatomammotropin (HCS).[235,254] Falling levels of these placental hormones near term suggest placental insufficiency and indicate a need for terminating the pregnancy.

In addition to the increased incidence of fetal anomalies and the high perinatal mortality associated with the diabetic pregnancy, the newborn infant of the insulin dependent (IDM) or gestational diabetic mother (IGDM) has a high incidence of neonatal morbidity. Such infants appear obese and plethoric; they are large for gestational age; they manifest visceromegaly involving the heart, liver and spleen; and they have increased stores of body fat.[249,255-257] Most of these changes can be attributed to fetal hyperinsulinemia. The IDM or IGDM is born with pancreatic islet cell hyperplasia and manifests fasting hyperinsulinemia and augmented insulin responses to glucose, amino acid and tolbutamide.[258-261] Thus, one of the major neonatal complications is hypoglycemia[248,249,259,260] but other complications, including hyperbilirubinemia, hyaline membrane disease, and hypocalcemia, are more commonly observed than in the normal newborn.

It is assumed that chronic fetal hyperglycemia associated with chronic maternal hyperglycemia is responsible for the fetal islet cell hyperplasia and hyperfunction. Insulin is an anabolic hormone, and chronic hypersecretion *in utero* (where hypoglycemia is prevented by maternal to fetal transport of glucose) results in increased fetal growth and increased fetal lipogenesis. However, the relatively high incidence of hyperbilirubinemia and respiratory distress in IDM or IGDM cannot be attributed to hyperinsulinism. These complications are more likely related to prematurity since most

IDM or IGDM are delivered early either spontaneously or electively.

It is now quite clear that the fetal morbimortality associated with pregnancy in diabetics can be reduced by careful management. It is particularly important to avoid acidosis, since this complication is associated with a high rate (about 30 percent) of fetal death *in utero*.[235] The lowest perinatal mortality occurs in patients in whom the blood glucose is kept closest to normal.[235] Since there is no increase in fetal hazard with maternal hypoglycemia, it is possible to control the diabetic or gestational diabetic subject fairly strictly. Moreover, one expects insulin requirements to increase progressively, especially near term. A decrease in insulin requirements in a diabetic woman in the later weeks of pregnancy is a grave prognostic sign for the fetus,[262] probably reflecting decreasing placental function. Oral hypoglycemic agents are not recommended for use during pregnancy.[235]

In the genetically predisposed subject who develops gestational diabetes mellitus, glucose tolerance characteristically improves after parturition and normal glucose tolerance is evident within three to five weeks postpartum. However, in about 30 percent of such women diabetes mellitus will develop within five years and 60 percent will be diabetic within 12 years.[263,264] Moreover, White has shown that 7 percent of the infants of diabetic mothers have diabetes mellitus by age 20 years.[263] Thus, although diabetes mellitus in pregnancy carries only a small risk of maternal mortality, it is a serious risk to the fetus and the newborn, a major challenge to the physician and carries important prognostic implications.

Although the offspring of diabetic mothers are frequently obese, the offspring of non-diabetic obese mothers are usually not overweight. In a study of 99 obese children, Wolff[265] found that their birth weights were identical in frequency distribution to that of other children born in the same hospital. Bruch, in a study of childhood obesity, also noted that the birth weight of obese children was normal. In the large group of children studied by Mossberg,[266] there was a larger variance among the birth weight of obese children than among the normal group. Thus, most of the obese children fell in the normal group, but there appeared to be a group of obese children with birth weights which tended to be higher than would be expected from the variance of the normal birth weights.

The Role of Carbohydrate and Oral Agents in the Treatment of Diabetes Mellitus

WILLIAM D. ODELL, MD, PhD*

DIABETES MELLITUS may be treated by one or more of several means; these commonly include dietary manipulation, insulin, sulfonylureas and biguanides. While it is beyond the intent of this discussion to review the usual aspects of standard treatment of diabetes mellitus, we would like to comment on some recent information that modifies our usual approach.

Dietary therapy optimally consists of adjustment of body weight to ideal and a distribution of calories into three or four approximately equal portions. Before the advent of insulin, dietary therapy was the only means of treating diabetic patients; typically low carbohydrate, low caloric diets were utilized. Because of this experience in the pre-insulin era, relative carbohydrate restriction has been advocated since the advent of insulin. Certain recent observations in diabetics cast doubt on the usefulness of such restriction. In normal men, Himsworth[267] showed in 1935 that if the carbohydrate content of the diet were reduced, but calories maintained, carbohydrate tolerance was lessened. Conversely, increasing dietary carbohydrate raised carbohydrate tolerance.

Such observations, now more than 37 years old, have been amply verified in more recent studies published in 1967 and 1968 by Wales et al[268] and Ford et al.[269] Brunzell and his coworkers[270] in 1971 extended these studies to diabetic subjects. In a carefully controlled study, non-diabetic and diabetic persons ranging from 91 percent to 163 percent of ideal body weight were studied. All subjects ingested diets of 40 percent fat, 45 percent carbohydrate and 15 percent protein during control periods and no fat, 85 percent carbohydrate and 15 percent protein in the experimental periods. Surprisingly, fasting insulin concentrations, fasting glucose concentrations, glucose tolerance and integrated insulin secretion during glu-

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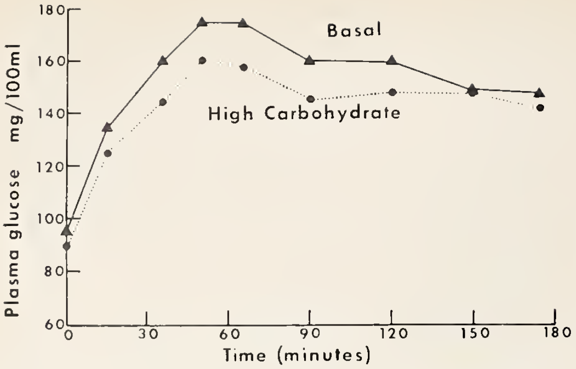

Chart 6.—The effect of high and low carbohydrate, isocaloric diets on the glucose tolerance curve of mild adult diabetic patients. Each subject received 100 grams of glucose at time zero minutes. (Published with permission from Brunzell et al.[270])

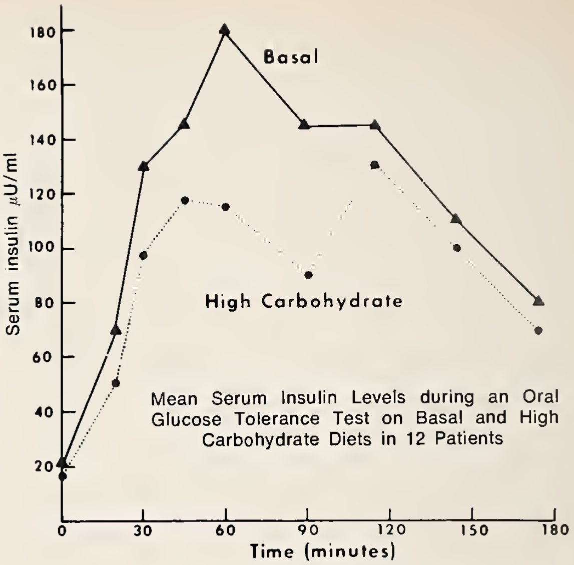

Chart 7.—The effect of high and low carbohydrate isocaloric diet on serum insulin concentrations during glucose tolerance tests. There are the same subjects depicted in Chart 1. (Published with permission from Brunzell et al.[270])

cose tolerance tests, all significantly fell on the high carbohydrate diet. Charts 6 and 7 taken from the publication of Brunzell's study show the changes in insulin concentration and glucose tolerance curve on high and low carbohydrate diets. In a similar study on obese subjects, Grey and Kipnis[37] found an increase in basal insulin secretion during a high carbohydrate diet and a reduction in insulin with a low carbohydrate intake. The studies of Grey and Kipnis are in contrast to those of Brunzell and coworkers, but one group studied obese patients, the others a mildly obese or non-obese population.

These two studies might lead us to the following conclusions:

1. Obese subjects are not benefited by high carbohydrate diets. However, since the obese diabetic should be treated with total calorie restriction and reduction of weight to ideal, this would not appear to be of practical importance.
2. The non-obese or mildly obese diabetic will show small improvements in carbohydrate tolerance, associated with lower insulin secretion when placed on generous carbohydrate but isocaloric diets. Certainly no need for carbohydrate restriction is evident. Whether this is associated with long term benefit is unknown.

For many years there has been a search for the ideal oral hypoglycemic agent. Based upon present knowledge, such an agent would duplicate the biochemical and physiological actions of insulin. While no ideal agent has been found, two categories of oral agents have come into common usage: the sulfonylureas and the biguanides. While there is little reason to believe these agents perfectly mimic insulin action, we as physicians have come to believe that because they lower blood sugar, they are of benefit in treatment of diabetes mellitus.

As to the sulfonylureas, it is commonly believed that the mechanism of action is to stimulate release of endogenous insulin. If this were the long-term effect of these drugs, they indeed might be expected to be of benefit. However, while the acute administration of sulfonylureas to animals or humans certainly stimulates insulin release, there appears to be no evidence that long-term treatment with them is associated with increased insulin secretion measured as either basal insulin concentration or as insulin secretion in response to carbohydrate loading. As a matter of fact, as will be discussed in further detail later, these drugs do not appear to maintain lowered blood glucose in diabetic subjects when used over a long period.[271-277]

Biguanides probably act in two ways to lower blood sugar in diabetics: (1) by impairing gluconeogenesis; (2) by inhibiting aerobic glycolysis and thus increasing anerobic glycolysis by peripheral tissues, predominantly muscle.[271-273] In the dosage normally used, they do not affect blood sugar in non-diabetics. While both agents lower blood sugar, it may still be legitimately asked whether they benefit the patient. Stated in another way, few patients who may be treated with either sulfonylureas or biguanides alone have difficulties with diabetic acidosis. While some acute symptoms such as polyuria, polydipsia or vaginitis may be beneficially affected by oral agents, in general one is treating the patient in the belief that the incidence of long-term vascular, or neurological complications of diabetes mellitus will be decreased by lowering blood sugar.

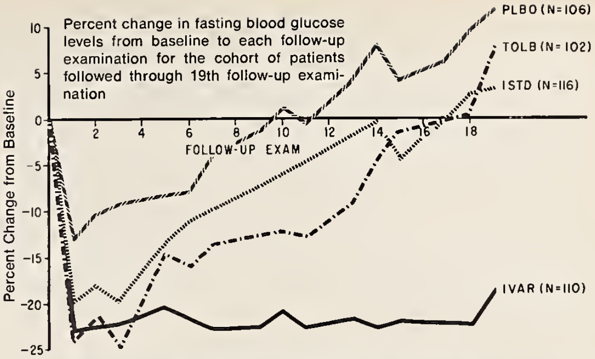

Chart 8.—Changes in blood glucose observed in four of the UGDP experimental groups. (Reproduced with permission from UGDP II, Mortality Results, 1971.)

A long-term study, the University Group Diabetes Program (UGDP) was initiated in 1958 in an attempt to assess this belief.[224-277] Twelve separate diabetic clinics treated adult onset diabetic patients, who by selection had sufficiently mild diabetes that they might be treated with diet alone. Patients recruitment began in 1961 and was completed in 1966. The patients studied ranged in age from 20 to 79; the majority were age 40-64, and the average was 53. There were 733 women and 294 men; 31 percent were hypertensive; 13 percent had serum cholesterol over 300 mg per 100 ml; 46 percent had one or more cardiovascular risks (hypertension, history of digitalis use, electrocardiographic abnormalities or serum cholesterol over 300 mg per 100 ml); 32 percent of the men and 10 percent of the women had arterial calcification in the right lower limb (which was arbitrarily selected for x-ray examination). However, it was not known which patients smoked. All patients had had the initial diagnosis of diabetes mellitus made within one year of entry into the study. Patients were randomly assigned to one of five groups listed in Table 17. Neither the patient nor the physician was aware whether the patient was receiving placebo, tolbutamide or biguanides. As is evident from the design, only one sulfonylurea (tolbutamide) was studied and it is not known whether others would give similar results.

This cooperative study has been evaluated in a series of publications published in the past three years. Several surprising results were observed: (1) The most publicized was that patients receiving sulfonylureas had an *increased* risk from cardiovascular death when compared with those receiving placebo. The increase exceeded the 95 percent confidence limits by the sixth year of treatment. (2) Less well publicized but perhaps of greater importance was that insulin therapy at fixed dosage or in variable dosage did not significantly reduce mortality from cardiovascular deaths.

Charts 8, 9 and 10 are reproduced from this

TABLE 17.—*Number and Percent Dead by Cause of Death*

	Placebo	*Tolbutamide*	*Insulin, Standard*	*Insulin, Variable*
Number at Risk of Death	205	204	210	204
Cardiovascular causes				
1. Myocardial infarction	0	10	3	2
2. Sudden death	4	4	4	5
3. Other heart disease	1	5	1	2
4. Extracardiac vascular disease	5	7	5	3
ALL CARDIOVASCULAR CAUSES	10	26	13	12
Noncardiovascular causes				
5. Cancer	7	2	4	2
6. Cause other than 1-5	1	2	2	3
7. Unknown cause	3	0	1	1
ALL CAUSES	21	30	20	18
Percent dead from				
Cardiovascular causes	4.9	12.7	6.2	5.9
All causes	10.2	14.7	9.5	8.8
P values*				
Cardiovascular	..	0.005	0.56	0.65
All causes	..	0.17	0.81	0.62

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*Based on Chi-square tests of significance (1 degree of freedom) of drug-placebo comparisons of the number dead. From the University Group Diabetes Program.[276]

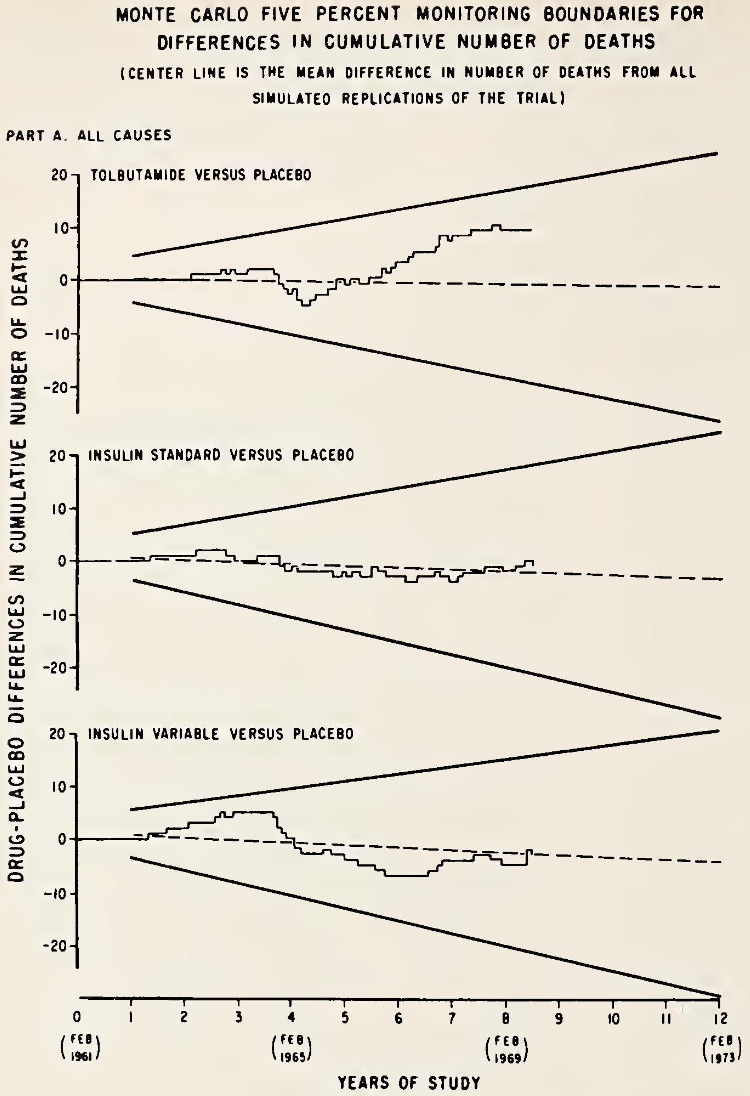

Chart 9.—The number of deaths occurring from all causes in the insulin variable, insulin standard, placebo and tolbutamide groups of the UGDP study shown as drug-placebo comparisons. The solid diagonal lines enclose the 95 percent statistical limits of differences—that is, when the experimental data lie outside these limits, the drug effects are significantly different from placebo effects at the p = or <0.05 level. Deaths from all causes were not different in the two groups at this level.

study and depict these data. The blood sugar fell at onset of therapy in all groups (including the placebo group) but remained significantly below control values only in the variable insulin group. In all other study groups, blood sugar gradually returned toward control levels and by the tenth to eighteenth follow-up examination had returned to control levels. Enrollment in the biguanide study group was initiated later than in the sulfonylurea group. The results for the phenformin group have been reported in preliminary form.[277] Phenformin was administered in a dose of 100 mg per day, half of it given before breakfast and half before the evening meal. The results indicated that this treatment group also had a significantly increased mortality when compared with diet therapy alone or with the two insulin treatment groups, both in terms of cardiovascular causes and in terms of deaths from all causes. Chart 11 depicts these data. Chart 12 shows the blood sugar measurements at the follow-up examinations which indicate as for tolbutamide, insulin in fixed dosage and placebo that these measurements return to control values after an initial beneficial response.

Such a study is obviously extremely difficult to perform. It is expensive, requires many years and great cooperation from the patients. At least one similar study is under way abroad. Confirmation or rebuttal of these important findings is essential. At least two detailed statistical reviews of these important studies have been made. Shor[278] pointed out that no assessment of cigarette smoking was made in any group and raises the question of whether this cardiovascular risk factor may not have been maldistributed among the groups. He said that his detailed analysis of preliminary un-

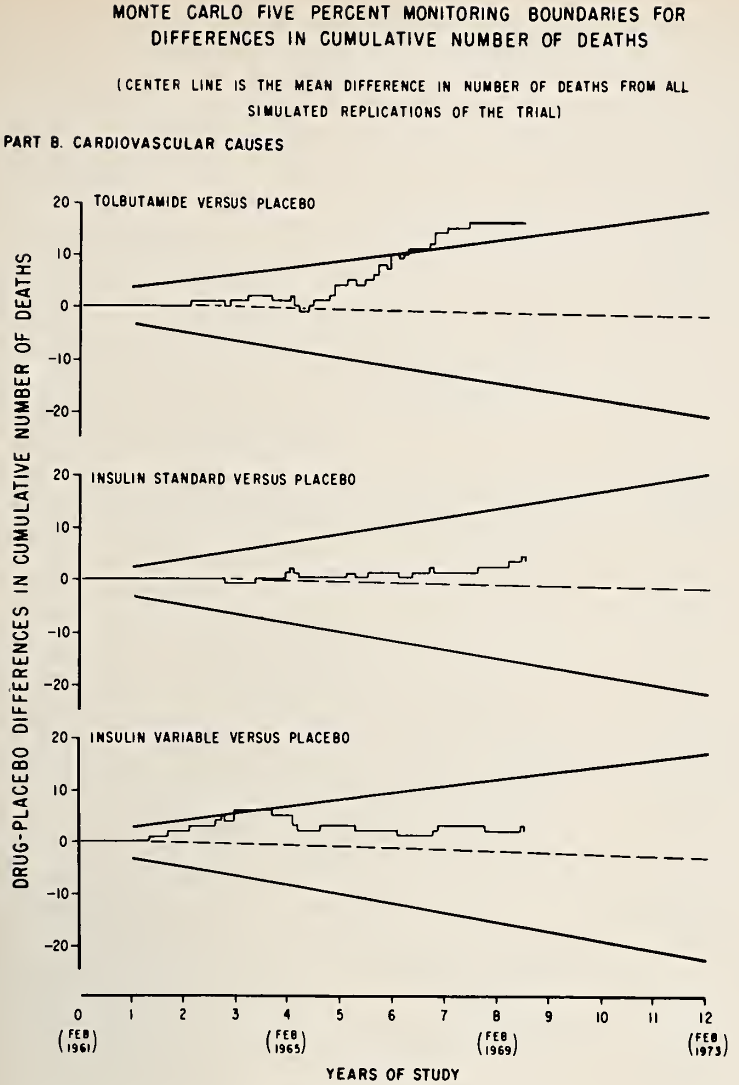

Chart 10.—Cardiovascular deaths plotted as in Chart 4. Note that between six and seven years of study, significantly more cardiovascular deaths had occurred in the tolbutamide group.

published records of the UGDP study revealed that the tolbutamide group had many more people with significant cardiovascular risk factors. For example, this group had almost three times as many patients with cholesterol levels over 300 mg per 100 ml, almost twice as many with significant electrocardiogram abnormalities, and more people who were white male and over 55. Cornfield,[27] in a detailed rebuttal, however, pointed out that if one analyzes only patients having no known cardiovascular risk factors, the excess of cardiovascular deaths in the tolbutamide group still stands out. The percent of cardiovascular deaths becomes 2.6 for placebo, 10.0 for tolbutamide, zero for insulin standard and zero for insulin variable. It thus appears that the validity of the conclusions cannot be settled with polemics; confirmatory, carefully designed long-term studies are needed. However, it appears clear then that there is little data to support the concept that prolonged treatment with oral hypoglycemic agents decreases the incidence of the long-term complications of diabetes. A number of less well controlled retrospective studies have indicated that well controlled insulin-treated diabetics may have less morbidity and mortality than poorly controlled insulin-treated subjects. Therefore, our personal philosophy based upon present data for treatment of adult diabetics at Harbor General Hospital might be summarized as follows:

1. If the patient is even mildly obese, reduce body weight to ideal and treat with dietary means thereafter.

2. If additional therapy is needed to gain good control or to abolish acute symptoms, use insulin in a variable dose. Attempt to maintain blood

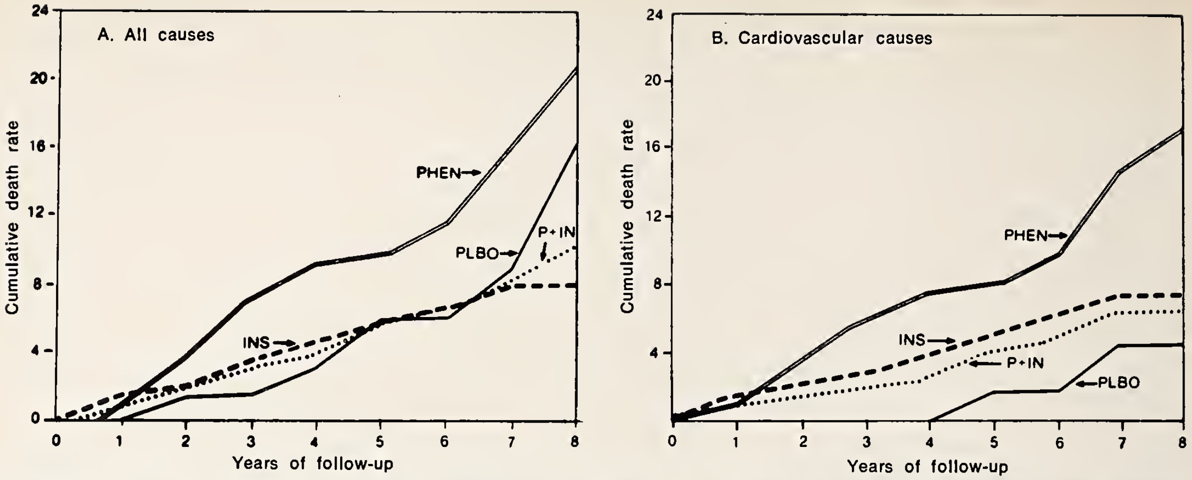

Chart 11.—Results of UGDP study with phenformin. The deaths from phenformin were increased when analyzed both in terms of all causes and from cardiovascular causes. (Reproduced from UGDP IV, 1971.)

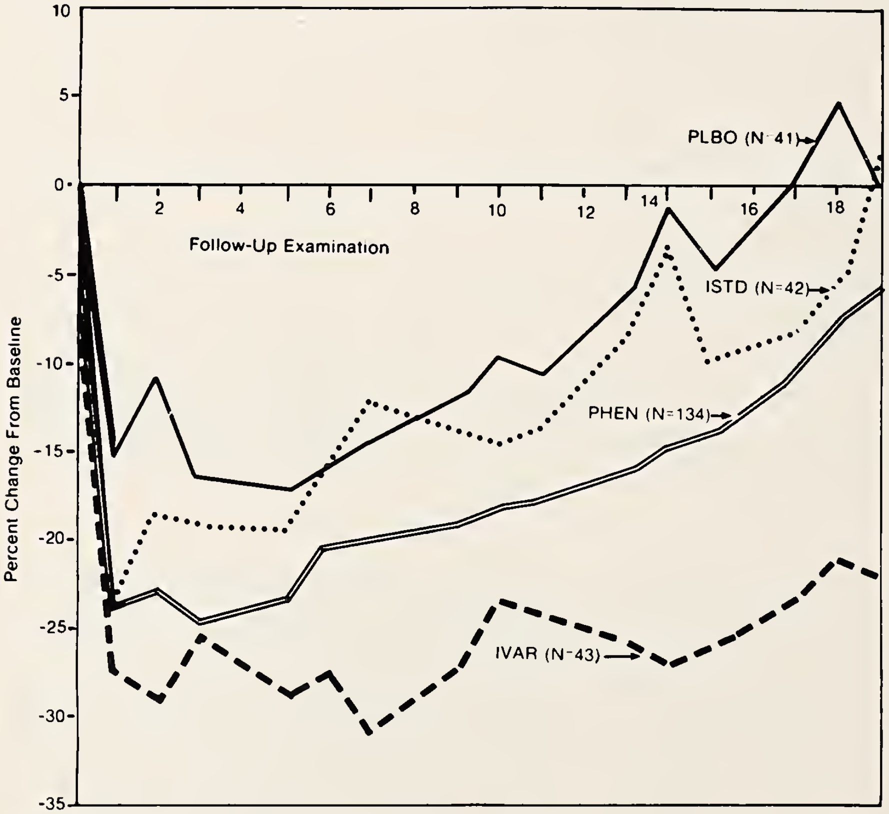

Chart 12.—Effects of phenformin on blood sugar concentrations. (Reproduced from UGDP IV, 1971.)

sugar as close to normal as possible at all times.

3. In selected patients having symptoms of polyuria, polydipsia or vaginitis, who, after complete discussion, refuse or are unable to take insulin, initiate therapy with sulfonylurea or biguanide, recognizing that in all probability only acute symptoms are alleviated and that long-term complications are probably not diminished and may be increased in frequency.

Of greater importance than the above, however, is the resounding message from this study that we are not treating diabetes mellitus effectively by any means. Continued research on the pathogenesis of diabetes mellitus and search for more effective means of treatment are clearly needed. The necessity of carefully controlled clinical experiments involving large numbers of human subjects is clear. Although individual rights must be safeguarded and careful peer review of all human research is essential, questions such as those the UDGP study attempts to answer cannot be settled in other ways.

Discussion

Following the Conference, physicians in the audience asked questions of members of the panel.

Question: Dr. Odell, in your discussion of the changes in glucose tolerance with carbohydrate diets, was there statistically significant difference in glucose tolerance in the subjects after feeding the high carbohydrate intake?

DR. ODELL: There were no statistically significant data on these points. Moreover, there is little evidence that carbohydrate restriction improves the life expectancy or well being of the diabetic as evidenced by the results of the UGDP study.

DR. FISHER: I would only add that carbohydrate restriction in the diabetic is of importance in those individuals who have a tendency to carbohydrate-induced elevations in the serum lipid, that is, the Type IV hyperlipoproteinemia which was frequently carbohydrate inducible.

Question: Dr. Swerdloff, why are patients in hyperosmolar coma not in shock?

DR. SWERDLOFF: It is clear from the data we have reviewed that patients in hyperosmolar coma are indeed water and electrolyte depleted. They are maintained out of shock, however, by preservation of the blood volume due to the high concentrations of glucose and its function as an intravascular osmotic molecule.

Question: Dr. Swerdloff, should one correct the fluid deficiencies first, before correcting the hyperglycemia, in patients with hyperosmolarity?

DR. SWERDLOFF: It is imperative to treat with fluid replacement. There has been an argument over the past several years as to whether hypotonic or normal physiological solutions should be used for fluid replacement. On the basis of the studies of Arieff, which we quoted, current evidence would suggest that the use of hypotonic solutions is preferable. In the Arieff studies, the patients who were treated with hypotonic solutions and who died did not have evidence of cerebral edema. This would indicate that the use of hypotonic solutions does not produce cerebral edema, which had been the major fear in its use.

Question: If the polyol pathway is responsible for the vascular complications in patients with diabetes, then a similar degree of vascular disease ought to be seen in patients with hyperglycemia secondary to pancreatitis. Has this been observed?

DR. ODELL: A hyperglycemia will cause damage in experimental animals but the answer to your question is not at present clear.

Question: In the UGDP studies, cardiovascular events were not different but deaths were increased in patients treated with tolbutamide. Why?

DR. BRAY: What you say about the difference between deaths being significant but cardiovascular events not being different is true. One suggestion has been that treatment with tolbutamide, and for that matter phenformin, impairs the ability to respond on the part of the host. In the patient treated with these drugs a cardiovascular event is thus more likely to be fatal than in patients with comparable events who were not treated with the drug. Whether this explanation is the true one or not must await additional investigation.

Question: Dr. Sperling, both lysine and arginine stimulate insulin, but do they lower the blood sugar?

DR. SPERLING: Amino acids increase glucagon as well as insulin. The rise in glucagon stimulates gluconeogenesis and glycogenolysis and thus prevents the hypoglycemia effects of insulin becoming manifest.

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Refer to: Drug-induced lung disease: The price of progress—Medical Staff Conference, University of California, San Francisco. Calif Med 119:48-55, Oct 1973

Drug-Induced Lung Disease: The Price of Progress

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *It has been a tradition at this institution to have our chief residents give the Medical Staff Conference just before their departure. Today, Dr. Stauffer will review what is known about drug-induced lung disease.*

DR. STAUFFER:† Fifty years ago relatively few drugs were available for the treatment of disease and most physicians were familiar with their adverse effects. Accordingly, drug-induced diseases were relatively uncommon. In the 1973 Physicians Desk Reference, approximately 6,000 drug products representing over 2,500 pharmaceuticals manufactured by 241 different drug companies are listed. As more and more drugs come onto the market, the incidence of drug-induced reactions increases.[1] Factors contributing to iatrogenic drug problems include an increased use of drugs by all levels of society, eagerness of physicians, stimulated by colorful drug ads and charming salesmen, to try new drug products, and failure of health personnel to recognize, acknowledge and report adverse drug reactions.

Let us examine briefly the magnitude of the problem of adverse drug reactions. Approximately 5 percent of hospital admissions are for treatment of iatrogenic disease (Table 1).[2,3] In a referral institution such as ours this number is probably much higher. One prospective drug surveillance

TABLE 1.—*Statistics Emphasizing the Magnitude of the Problem of Adverse Drug Reactions*

1. 5 percent of hospital admissions are for treatment of drug-induced disease
2. 18 percent of hospitalized patients develop adverse drug reactions
3. 3 percent of hospital deaths are drug-related
4. The "average" hospital patient receives 6 to 10 different drugs, some receive 15 to 20
5. USPHS estimated that 1.3 million therapeutic misadventures occur each year (1967)—twice the number of Americans treated for cancer
6. $3 billion expenditure for hospital care of adverse drug reactions

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study showed that in a large general hospital adverse drug reactions developed in up to 18 percent of patients.[4] Approximately 3 percent of hospital deaths have been reported to be drug-related.[5,6] The hospital patient receives an average of six to ten different drugs, and some receive as many as 15 to 20.[7] In 1967, the United States Public Health Service estimated that 1.3 million therapeutic misadventures occur each year, which is about twice the annual number of Americans treated for cancer. It was estimated that in 1971 a million and a half people had adverse drug reactions severe enough to require admittance to hospital, at a cost of three billion dollars.[8]

Adverse drug reactions in the lung represent only a small fraction of the total problem. Pulmonary complications ascribed to drug therapy represent less than 5 percent of all adverse drug reactions among patients in hospital.[2] Our inability to recognize adverse reactions in the lung may account for this reported low frequency. Whereas much is known about drug-induced diseases of the liver, kidney, heart, brain and bone marrow, relatively little attention has been directed toward drug-induced lung disease. In 1972 Rosenow drew attention to about 50 different drugs that have been implicated in iatrogenic lung disease.[9] Most of them have appeared on the market during the last 15 to 20 years. The role of other drugs has also been discussed in the literature.[10-13]

The classification of pulmonary drug reactions is the same as that for any organ system. Reactions may result from overdosage, from an excessive effect of usual therapeutic doses, from unavoidable side effects, or from effects due to a second pharmacologic action of the drug. Most commonly, however, reactions are of the idiosyncratic or hypersensitivity type. Finally, interactions among drugs may lead to adverse reactions.

In most adverse drug reactions involving the lung, the mechanisms of tissue injury remain obscure. Perhaps one explanation for this is that relatively few cases of drug-induced lung disease have been studied pathologically. In addition, the lung is limited in the scope of its response to injury, both from clinical and pathological standpoints. Consequently, the manifestations are rarely specific for a given drug. Finally, adverse pulmonary drug reactions may mimic respiratory disease or disease of other causes and therefore go unnoticed.

Drugs causing lung disease can be conveniently classified according to the type of end-response of the lung as listed in Table 2. Nevertheless, it should be emphasized that one drug may act through several mechanisms to yield more than one of these patterns. Let us examine the drugs implicated in each of these categories.

TABLE 2.—*Patterns of Drug-Induced Lung Disease*

1. Pulmonary fibrosis
2. Pulmonary edema
3. Asthma
4. Hypersensitivity reactions
5. Respiratory failure
6. Opportunistic infections
7. Pulmonary embolism
8. Pulmonary infiltrates
9. Mediastinal and hilar disease
10. Fever
11. Aspiration pneumonia
12. Systemic lupus erythematosus
13. Nitrofurantoin lung disease
14. Oxygen toxicity
15. Miscellaneous

TABLE 3.—*Drugs That May Cause Pulmonary Fibrosis*

Busulfan (Myleran®)
Cyclophosphamide (Cytoxan®)
Hexamethonium
Mecamylamine (Inversine®)
Pentolinium (Ansolysen®)
Methysergide (Sansert®)
Bleomycin
?Diphenylhydantoin (Dilantin®)
Nitrofurantoin (Furadantin®)

Pulmonary Fibrosis (Table 3)

Busulfan, an alkylating agent used in the treatment of chronic myelocytic leukemia for the last 20 years, for the first seven years of its existence was thought to be free of toxic effects. Toxic reactions now described include marrow suppression, gonadal suppression, increased skin pigmentation, an Addisonian-like syndrome, and interstitial pulmonary fibrosis, which is the most serious complication. A fairly typical histological pattern of pulmonary fibrosis may evolve after the therapy has been continued for a period as short as nine months or as long as eight years.[9] The histological abnormality is an organizing fibrinous edema with hyperplasia of atypical type II granular pneumocytes, the alveolar epithelial cells which produce surfactant. Therefore, intra-alveolar fibrosis may follow. This fibrotic process is often irreversible, despite discontinuation of the drug. Corticosteroid therapy is usually to no avail. Although severe restrictive lung disease, and even death, have been reported, the intra-alveolar edema and fibrosis are usually not severe enough

TABLE 4.—*Drugs That May Cause Pulmonary Edema*

Heroin (smack)
Methadone (Dolophine®)
Propoxyphene (Darvon®)
Hydrochlorothiazide (Hydrodiuril®)
Epinephrine (Adrenalin®)
Phenylbutazone (Butazolidin®)

to cause disability. An almost identical response has followed the use of cyclophosphamide, although this syndrome is also rare.[9,14]

One of the first reports implicating drugs as a cause of lung disease came in 1954 with a report of pulmonary fibrosis secondary to hexamethonium therapy for hypertension.[15] Hexamethonium is chemically related to busulfan, but the histological response in the lung differs in that atypical type II pneumocytes are absent. The newer autonomic blocking agents were also found to possess fibrogenic capability. Pentolinium and mecamylamine both cause pulmonary fibrosis in some patients.[16,17] With any of the ganglionic blocking agents, symptoms usually appear in susceptible persons during the first year of therapy.

Methysergide produces a number of adverse reactions, including retroperitoneal fibrosis and pleuropulmonary fibrosis.[18,19] In addition, methysergide is the only drug known to produce a chronic pleural effusion.[9] Possibly the fibrotic reaction is related to the vasoconstrictor effect of the drug, but this is only speculative. Fibrosis may also involve the mediastinum and heart; and, indeed, aortic, mitral and coronary ostial involvement have all been reported.[18,20] The retroperitoneal, cardiac or pleuropulmonary fibrosis usually appears after more than one year of therapy with methysergide and regresses when the drug is discontinued. Bleomycin, a mixture of antibiotic polypeptides used in the treatment of advanced Hodgkin's disease and a number of other tumors, may lead to interstitial pneumonitis and fibrosis with pulmonary insufficiency.[21] The mortality rate is reportedly 2 to 8 percent.[21] Diphenylhydantoin was once thought to cause diffuse pulmonary fibrosis but later observations have not been confirmatory.[22] Nitrofurantoin is a rare cause of chronic pulmonary fibrosis.

One must be cautious in attributing pulmonary fibrosis to drugs, especially in patients with cancer. These patients are subject to other causes of pulmonary fibrosis, such as opportunistic infection, neoplastic involvement of the lung and radiation therapy.

Pulmonary Edema

Table 4 lists the drugs that may produce pulmonary edema. Complications of heroin abuse include pulmonary edema as well as septic pulmonary emboli, pneumonia, lung abscess, respiratory failure, aspiration, and pulmonary hypertension.[23] Characteristically, patients with heroin-induced pulmonary edema have acidosis, hypercapnia, hypoxia, and often hypotension.[24,25] Complications include pulmonary hypertension, cardiac arrhythmias of all types, pneumonia, possibly chronic lung disease, and death. The pathogenesis of this entity is obscure, although a variety of theories, including hypersensitivity, depression of the respiratory center, and direct toxic damage to pulmonary capillaries, have been proposed.[25] The best concept is that respiratory depression induces hypoxia, which increases capillary permeability, leading to fluid extravasation and pulmonary edema. It is ironic that methadone, used to treat heroin addiction, may also cause pulmonary edema, although it is not structurally similar to heroin.[26,27] Propoxyphene is structurally related to methadone and is a known cause of pulmonary edema.[28] Three cases of acute pulmonary edema secondary to ingestion of hydrochlorothiazide have been reported, and in one a probable allergic basis was proposed because of recurrence after challenge testing.[29] Pulmonary edema following accidental overdose of epinephrine in the surgical setting has been frequently reported.[30] Two cases of acute pulmonary edema in elderly patients precipitated by the use of phenylbutazone underscore the well known antidiuretic effect of this drug, leading to salt and water retention.[31]

Asthma

Many drugs have been reported to cause bronchospasm[11] (Table 5). Important mechanisms include irritation of the airways, type I or immediate hypersensitivity, and beta adrenergic blockade. Important drugs in this list include penicillin, aspirin, propranolol, and several muscle relaxants. Interestingly, three drugs used in the treatment of bronchospasm and bronchitis may exacerbate these conditions. Acetylcysteine, a mucolytic agent, may in fact increase airway resistance through mechanisms not yet understood.[32,33] Disodium cromoglycate, a promising new drug used in Europe in the treatment of asthma, may induce bronchospasm in some patients. This often necessitates concomitant use of aerosolized isoproterenol.[34] Isoproterenol has been implicated as a cause of death in patients with asthma.[35]

Hypersensitivity Reactions

Three drugs, procarbazine, hydrochlorothiazide and pituitary snuff, have been fairly well documented to injure the lung through a hypersensitivity reaction. Most physicians encountering pulmonary drug reactions have been reluctant to subject their patients to controlled challenges with drugs and with good reason. Consequently, our understanding of the hypersensitivity basis of pulmonary drug reactions is limited. Three cases of hypersensitivity to procarbazine have been reported.[36] Hydrochlorothiazide, as previously mentioned, has produced recurrent pulmonary edema on controlled challenge with the drug.[29] Inhalation of pituitary snuff produces a characteristic response with progressive dyspnea, diffuse pulmonary infiltrates, and eosinophilia. The reaction is typical of extrinsic allergic alveolitis, and precipitating antibodies to pituitary components have been demonstrated in the sera of symptomatic patients.[37] This typical type III hypersensitivity reaction is the best example of hypersensitivity pneumonia in drug-induced lung disease. Type III reactions to pituitary snuff have been averted since the development of synthetic lysine vasopressin. Nitrofurantoin might be added to this brief list, but as we shall see, the hypersensitivity basis remains to be confirmed.

TABLE 5.—*Drugs That May Cause Asthma*

Penicillin
Tetracycline
Erythromycin
Neomycin
Streptomycin
Griseofulvin
Cephaloridine (Keflin®, Loridine®)
Ethionamide (Trecator®)
Monoamine oxidase inhibitors (Parnate®)
Radio-opaque organic iodides
Local anesthetics
Mercurials
Vitamin K
Bromsulphalein
Sodium dehydrocholate (Decholin®)
Iron dextran (Imferon®)
Prostaglandin F_2A
Pentazocine (Talwin®)
Indomethacin (Indocin®)
Nitrofurantoin (Furadantin®)
Reserpine
Antisera
Vaccines
Allergenic extracts
Aspirin
Histamine phosphate
Methacholine (Mecholyl®)
Acetylcysteine (Mucomyst®)
Calcium gluconate
Disodium cromoglycate (Cromolyn®)
Polymyxin B
Isoproterenol (Isuprel®)
Propranolol (Inderal®)
Pituitary snuff
?Synthetic lysine vasopressin
Hashish
Succinylcholine
d-Tubocurarine
Gallamine (Flaxedil®)

TABLE 6.—*Drugs That May Cause Respiratory Failure*

Central Nervous System Depression	*Respiratory Muscle Paralysis*
Sedatives and hypnotics	Neomycin
Oxygen in patients with hypercapnia	Streptomycin
Heroin	Kanamycin
Alcohol	Gentamicin
THAM	Polymyxin B
Antihistamines	Colistin
Anesthetics	Succinylcholine
	Curare, quinine, and quaternary ammonium compounds

Respiratory Failure

Drug-induced respiratory failure might occur through several mechanisms, including central nervous system depression and respiratory muscle paralysis (Table 6). Essentially all sedatives and hypnotics taken in excess depress the respiratory center. The injudicious use of oxygen in patients with carbon dioxide retention is a well known hazard. Heroin and alcohol are potent central nervous system depressants. Tris-hydroxymethylaminomethane (THAM or TRIS) may be an effective buffering agent in severe respiratory acidosis, but the reduction in carbon dioxide tension which follows its use may remove the carbon dioxide stimulus to breathing in some patients, and hypoventilation and hypoxia may follow.[13] Many antihistaminics, such as diphenhydramine, have central depressant effects especially when taken in excess. Respiratory depression has followed the long or excessive use of both general and local anesthetics. Neuromuscular blockade and respiratory paralysis with hypoventilation have followed the administration of a number of antibiotics.[13]

Opportunistic Pulmonary Infections

Opportunistic pulmonary infections are well known hazards of the use of corticosteroids and cytotoxic and immunosuppressive agents. Common opportunistic organisms include bacteria, fungi, cytomegalovirus, and Pneumocystis carinii.

Pulmonary Embolism

Pulmonary thromboembolism may complicate the use of oral contraceptives. Other agents have also been implicated, including iodized oils which are used in lymphangiography and several other contrast studies. Interstitial lung disease has resulted with sufficient frequency from the administration of these oils that pulmonary function testing with diffusion capacity measurements is required before lymphangiography is performed.

TABLE 7.—*Drugs Associated with Pulmonary Infiltrates*

With Eosinophilia	*Without Eosinophilia*
Aminosalicylic acid (PAS)	Methotrexate (Amethopterin®)
Isoniazid (INH)	Azathioprine (Imuran®)
Penicillin	Paraquat
Nitrofurantoin (Furadantin®)	Illicit drugs
Aurothioglucose (Solganal®)	Procarbazine (Matulane®)
Mephenesin carbonate (Tolseram®)	
Poison ivy allergen	
Chlorpropamide (Diabinese®)	
Disodium cromoglycate (Cromolyn®)	
Aspirin	
Sulfonamides	
Imipramine (Tofranil®)	
Pituitary snuff	

Two patients with miliary metallic densities shown on chest x-ray films three to four years after the accidental intravenous injection of mercury have been reported.[38] Intravenous fluids may contain significant amounts of particulate matter including glass, plastics and rubber, and it has been postulated that pulmonary vascular disease and pulmonary hypertension may follow the administration of large volumes of these fluids.[9,39] Particles of talcum and cotton fibers have been found in the small pulmonary vessels of persons mainlining illicit drugs. This is a known cause of pulmonary vasculitis. Perhaps corticosteroids should also be added, since fatal fat embolism from steroid-induced fatty liver has been reported.[40]

Pulmonary Infiltrates

Nonspecific pulmonary infiltrates, especially in the lower lobe, may follow the administration of many drugs (Table 7). Eosinophilia appears to be a helpful differential point. There are many causes of pulmonary infiltrates with eosinophilia, the so-called "P.I.E. syndrome." This syndrome may occur in idiopathic form known as Loeffler's syndrome, or iatrogenically as a consequence of drug therapy. It is characterized by fever, dyspnea, cough and peripheral eosinophilia with transient patchy infiltrates and occasional pleural effusions noted on x-ray films of the chest. The mechanism of this reaction is unknown. PAS, isoniazid, penicillin, nitrofurantoin, aspirin and sulfonamides are the commonest causes of this reaction. It has also been reported with aurothioglucose, a gold preparation used in the treatment of rheumatoid arthritis. There have been single reports of P.I.E. syndrome due to mephenesin carbamate,[41] a muscle relaxant, and to chlorpropamide,[42] imipramine[43] and disodium cromoglycate.[44] Pulmonary infiltration with or without eosinophilia which may be fatal has been reported with methotrexate. Procarbazine, azathioprine and several illicit drugs, as well as paraquat, a herbicide, also produce pulmonary infiltrates.

Mediastinal and Hilar Disease

Up to 15 percent of patients with iatrogenic Cushing's syndrome have at least minimal widening of the mediastinum.[45] This finding is also seen in spontaneous Cushing's disease. Prominence of the epicardial fat pad may be a helpful diagnostic clue that steroids are responsible. Diphenylhydantoin is a well known cause of systemic lymphadenopathy but lymphadenopathy limited to the mediastinum or pulmonary hila is rare.[46] A reversible hilar and paratracheal lymphadenopathy has been reported in one patient receiving methotrexate.[47]

Fever

Several drugs implicated in lung disease produce fever with such regularity that they warrant especial mention. In the acute reaction to nitrofurantoin, moderate fever is an almost constant finding. Adverse pulmonary reactions to busulfan, cyclophosphamide, methotrexate, and procarbazine are almost always febrile reactions.

Aspiration Pneumonia

Inadvertant aspiration of a number of seemingly innocuous materials can cause pneumonia. Exogenous lipoid pneumonia has been well described following aspiration of a number of lipid-containing materials, including castor oil, nose drops, nose sprays, mineral oil, iodized oils used in bronchography, and, believe it or not, even Chapstick. The protracted use of mineral oil by elderly persons for relief of constipation has led to syndromes of acute and chronic pneumonia. A localized "granuloma" or so-called "paraffinoma" in these patients may simulate a neoplasm. Mineral oil, as is well known, is a drug which the patient frequently neglects to mention when a drug history is taken. This material is aspirated into the airway and usually does not produce symptoms or cough. Chapstick is a lipid-containing lip balm. The one reported case in which it was implicated was that of a 52-year-old bus driver who used it compulsively 20 or 30 times a day for 20 years and finally presented with acute lipoid pneumonia.[48] Aqueous bronchographic contrast media such as Hytrast® may cause aspiration pneumonia;[49] and one death due to this complication has been reported. The inhalation of talc, a microfine powder of magnesium silicate, is a hazard of childhood and may be fatal.[50]

Systemic Lupus Erythematosus

To date at least 27 drugs have been recognized as inducing systemic lupus erythematosus.[9-11] Among these, the ones listed in Table 8 are frequently used on our medical service. The pulmonary involvement includes acute and chronic pleuritis, pleural effusions, atelectasis and interstitial pneumonitis. Complete resolution usually occurs when the offending drug is discontinued.

TABLE 8.—*Drugs That May Cause Systemic Lupus Erythematosus*

Procaine amide (Pronestyl®)	Gold salts
Hydralazine (Apresoline®)	Diphenylhydantoin (Dilantin®)
Isoniazid (INH)	Mephenytoin (Mesantoin®)
Penicillin	Propylthiouracil
Tetracycline	Methylthiouracil
Sulfonamides	Thiazides
Streptomycin	Reserpine
Griseofulvin	Methyldopa (Aldomet®)
Aminosalicylic acid (PAS)	Oral contraceptives
Phenylbutazone (Butazolidin®)	Digitalis

Nitrofurantoin Toxicity

Almost 250 cases of pulmonary reactions to nitrofurantoin have been reported since 1959, but credit for the first report goes to Israel and Diamond, who first described pulmonary infiltration and pleural effusion with this drug.[53-55] No deaths have been reported. Other nitrofuran derivatives that have been administered to man do not produce a similar pulmonary reaction, and pulmonary disease does not develop in laboratory animals given nitrofurantoin. Both acute and chronic reactions to nitrofurantoin have been described. The acute reaction is much more common than the chronic one and is characterized by cough, fever, chills and shortness of breath appearing several hours to several days after therapy is begun. Approximately one-third of patients have eosinophilia. An acute nitrofurantoin reaction occasionally presents as asthma. Chest x-ray films usually reveal interstitial or alveolar infiltrates and often small pleural effusions. There are no published histological studies of the acute reaction. The acute changes usually resolve within two to three days after therapy is withdrawn, and there is no relationship between the acute and the chronic phases. The chronic phase, characterized by cough and dyspnea, appears six months to six years after therapy is begun. Rosenow described five cases in detail in 1968.[56] In all cases, diffuse bilateral infiltrates were present, most severe at the lung bases. Lung biopsy studies showed a nonspecific pattern of diffuse interstitial fibrosis and pneumonitis. Four of the five patients improved when the drug was discontinued and steroids given. The chronic phase is noteworthy for the absence of eosinophilia, fever and pleural effusion. Provocative tests have indicated that the nitrofurantoin reaction is probably a hypersensitivity reaction, although the exact nature of the response is not understood.

Oxygen Toxicity

Pulmonary oxygen toxicity was first described by Lavoisier in the 18th Century. Since then, oxygen toxicity has commanded a great deal of attention in the literature.[57-61] Oxygen is one of the most commonly prescribed drugs in the hospital. First, a note of caution is necessary. In cases in which death is ascribed to oxygen toxicity, the patients usually are already extremely ill. Invariably, they also suffer from other problems, including infection, congestive heart failure, overhydration, pulmonary embolism, tumors and a number of other surgical and medical illnesses. The postmortem findings in these patients usually demonstrate morphological characteristics that may be indistinguishable from those produced by oxygen toxicity alone. Nevertheless, it is now well established that prolonged oxygen therapy may cause progressive pulmonary injury. Although individual susceptibility varies greatly, definite signs of lung damage can be detected in patients breathing 100 percent oxygen for 24 to 48 hours. Probably at least 24 hours is necessary for lung damage to occur. With inspired oxygen concentrations in the range of 60 to 70 percent, a longer period is necessary. Inspired oxygen concentrations below 50 percent do not seem to injure pulmonary tissue directly, but impairment of tracheal mucus flow and inhibition of killing by alveolar macrophages do occur at these lower concentrations. Both an acute exudative phase and a chronic proliferative or fibrotic phase have been defined. Symptoms of the acute phase are throat irritation, nonproductive cough, substernal discomfort, low grade fever,

TABLE 9.—*Drugs Associated with Miscellaneous Reactions in the Lungs*

Polyarteritis:
- Iodides
- Arsenicals
- Mercurials
- Hydantoins
- Penicillin
- Guanethidine (Ismelin®)
- Gold salts
- Thiouracils
- Phenothiazines
- Sulfonamides
- Hydralazine (Apresoline®)

Pulmonary calcification:
- Calcium gluconate
- Vitamin D

Necrotizing vasculitis:
- Illicit drugs, ?corticosteroids

Pulmonary hypertension:
- Aminorex fumarate

Intrapulmonary hemorrhage:
- Anticoagulants

and increased secretions. Rales, rhonchi, and tubular breath sounds are present on physical examination, and after several days of breathing pure oxygen at normal atmospheric pressures profound respiratory distress may appear. Hypoxia and an increasing alveolar-arterial oxygen gradient are apparent. Within three to four days, x-ray films of the chest show small linear infiltrates which may become confluent. Pulmonary function tests at this stage may show decreases in vital capacity, lung compliance, and diffusing capacity. Pathologically, the earliest lesion is damage to capillary endothelial cells. A leakage of fluid into the interstitial space with resultant interstitial edema follows. Capillary congestion, intraalveolar hemorrhage, and fibrinous alveolar exudates may be seen at necropsy if the patient does not survive the exudative phase. If the oxygen exposure is not terminated, a proliferative phase with fibrosis and hyperplasia of type II granular pneumocytes may follow. This phase is probably irreversible once it has begun.

Treatment of oxygen toxicity is difficult because the greater the extent of oxygen-induced pulmonary injury, the more oxygen the patient needs to correct the arterial hypoxemia. Nevertheless, the only effective therapy is reduction of inspired oxygen concentration to less than 50 to 60 percent. Efforts should be made to keep the arterial oxygen partial pressure (pO_2) between 70 and 120 mm of mercury. However, it appears that normal arterial oxygen concentrations do not protect the lung from the adverse effects of high alveolar concentrations. Efforts should be made to improve the oxygen delivery to tissues, as well as to reduce tissue demands for oxygen. Vigorous tracheobronchial toilet, maintenance of adequate hemoglobin content in the blood, maintenance of cardiac output, and reduction of tissue demands for oxygen by treating fever, hyperthyroidism and other hypermetabolic states are all important. In animals with oxygen toxicity, increased survival time has been demonstrated with the simultaneous addition of such agents as adrenergic blocking drugs, chlorpromazine, THAM, and anti-oxidants.[57]

The molecular basis for oxygen toxicity remains a matter of controversy. The role of surfactant and other surface active phenomena is still in dispute. Most investigators have found decreased surfactant activity in oxygen-poisoned lungs, but whether this is an initiating factor or a secondary consequence of lung injury is not yet clear. Subsequently there appears to be an inactivation of key metabolic enzymes either through oxidation of sulfhydryl groups or formation of free radicals which then damage the enzymes. In some cases, lipid peroxidation of membranes may occur. The net result is cellular damage through interference with normal energy generating mechanisms and normal processes for maintenance of the cell. Why the capillary endothelial cell is the chief target is not clear.

Miscellaneous Reactions (Table 9)

A polyarteritis nodosa-like vasculitis in the lungs may follow the use of sulfonamides and many other drugs.[11] Pulmonary calcification has been reported after excessive intake of milk and alkali, high doses of vitamin D, calcium, and inorganic phosphate. Necrotizing vasculitis is a frequently described complication of the intravenous use of illicit drugs, especially amphetamines. Corticosteroids have been implicated in the vasculitis of rheumatoid arthritis, infrequently involving the lungs, although this association is not uniformly accepted. The introduction of aminorex fumarate, an anorectic drug widely used in the treatment of obesity in Switzerland between 1966 and 1968,[51,52] was followed by a 10- to 20-fold rise in the incidence of pulmonary hypertension, the pathogenesis of which is not clear. Fortunately, the drug was withdrawn from the market in 1968. Spontaneous pulmonary and intrapleural hemorrhage is an uncommon complication of anticoagulant therapy.

Awareness of the pulmonary complications of drug therapy—a problem that may become increasingly important—should result in their earlier recognition and successful treatment.

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Important Advances in Clinical Medicine

Epitomes of Progress—Internal Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Internal Medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Internal Medicine which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Internal Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, CA 94102

Ultrasound as a Non-Invasive Technique for Measuring Cardiac Performance and Diagnosing Cardiac Lesions

REPETITIVE SHORT PULSE BURSTS of ultra high-frequency sound can be directed into the chest, along a relatively narrow path, with partial reflectance of the sound at each interface of materials having different acoustic impedance or density. This principle has allowed the development of a safe, non-invasive means to record and analyze the motion of intracardiac structures. Echography of mitral valve motion shows a characteristic early diastolic and pre-systolic opening pattern which is grossly altered in mitral stenosis. The atrioventricular pressure gradient maintains the valve in the open position throughout diastole. The normal M-shaped pattern is thus converted to a square wave. The slope of the diastolic portion of this pattern and the leaflet excursion gauge the severity of stenosis and the pliability of the leaflets, respectively.

Echography has provided a valuable screening test for mitral stenosis and differentiates true stenosis from the Austin-Flint murmur and intracardiac tumors which may masquerade as valvular disease. Patients with muscular subaortic stenosis have an abnormal systolic motion of the anterior mitral leaflet toward the left ventricular outflow tract. This abnormal systolic motion is well seen echographically and provides a non-invasive diagnostic test for this condition. Posterior systolic motion of the mitral valve is recorded in the prolapsing posterior leaflet syndrome of non-rheumatic mitral regurgitation.

It is possible to direct the ultrasonic beam along a path including the chest wall, right ventricle, interventricular septum, and left ventricle, intersecting the posterior left ventricular wall just below the free edge of the mitral valve, and just above the tips of the papillary muscle. This beam orientation currently is used most to define the presence or absence of pericardial fluid, the thickness of the posterior left ventricular myocardium and the size of the ventricular chambers. The bedside diagnosis of pericardial effusion has been very reliable since the development of a standardized technique for the examination. This latter method has great utility in acutely ill patients or in emergency situations. Increased relative size of the right ventricle and abnormal interventricular septum motion are observed in conditions with diastolic volume overload of the right ventricle such as atrial septal defect, anomalous pulmonary venous return and tricuspid regurgitation. End-diastolic and end-systolic left ventricular diameters measured echographically may be used to calculate total left ventricular stroke volume and ejection fraction. If there is valvular regurgitation, the difference between total ventricular stroke volume and effective or forward stroke volume measured by the Fick method gives a quantitative estimate of the degree of regurgitation. Also, echographically determined velocity of left ventricular epicardial motion has been used as an index of ventricular contraction.

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Combination Drug Therapy in Metastatic Carcinoma of the Breast

THE USE OF COMBINATIONS of cytotoxic agents in the treatment of advanced cancer has proved to be superior to single agent therapy in clinical response and survival in leukemia and lymphoma. Recently, encouraging results have been obtained in other metastatic solid tumors.

Metastatic carcinoma of the breast which is unresponsive to or has relapsed from endocrine therapy has recently been shown to be quite responsive to a five-drug combination including 5-fluorouracil, methotrexate, cyclophosphamide, vincristine and prednisone, with good to excellent responses in more than 70 percent of patients. Similar high complete response rates have been obtained with modifications of this therapy in several institutions. We have obtained good to excellent responses in 68 percent of patients treated with 5-fluorouracil, methotrexate and cyclophosphamide. Toxicity from this drug combination has been low.

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Hypothalamic Hypothyroidism

THE SIMULTANEOUS OCCURRENCE of a low thyroid hormone level and a normal or low serum level of thyroid stimulating hormone (TSH) in a patient with hypothyroidism establishes the diagnosis of secondary hypothyroidism. The administration of thyrotropin releasing hormone (TRH), which is normally synthesized and released by the hypothalamus, enables the physician to distinguish between pituitary and hypothalamic causes of hypothyroidism. TRH will normally cause the release of TSH from the pituitary gland. This will occur even in the face of an elevated TSH level in patients with primary hypothyroidism. If the thyrotroph cells of the pituitary gland are destroyed, no rise in TSH occurs. When the hypothalamus does not synthesize or release TRH, the administration of exogenous TRH will result in prompt rise of serum TSH. To date, the cases reported of pituitary hypothyroidism have been associated with pituitary tumors, hypophysectomy or postpartum necrosis of the pituitary gland. Hypothalamic hypothyroidism, on the other hand, may either be idiopathic or result from demonstrable hypothalamic disease, and it accounts for most cases previously attributed to an idiopathic pituitary TSH deficiency. The TRH stimulation test can therefore aid in more accurate localization of certain destructive processes of the central nervous system.

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Indications for Lavage in the Treatment of Bronchopulmonary Disease

SEGMENTAL LUNG LAVAGE has been attempted for many years in the treatment of a variety of pulmonary diseases. In recent years, a technique using "volume-controlled lung lavage" has been reported to be of value in certain circumstances.

With the use of a Carlens tube, one can isolate the two lungs, allowing for ventilation of one lung while lavage is being carried on in the other. Normal saline solution is used as the basic lung irrigant. Monitoring of serial arterial blood gas samples during the lung lavage is important to insure that an adequate arterial PO_2 is being maintained.

"Volume-controlled lung lavage" has been used in the treatment of pulmonary alveolar proteinosis, chronic bronchitis, cystic fibrosis, bronchial asthma, pneumonia, desquamative interstitial pneumonitis, bronchiectasis, Goodpasture's syndrome, and accidental radioactive particle inhalation.

In alveolar proteinosis, lung lavage consistently results in improvement, and in fact, may be lifesaving. Multiple lavages may be required in the treatment of this disorder.

In "status asthmaticus," lack of appropriate response to therapy may be due to diffuse plugging of airways with thick tenacious mucus. Removal of these plugs by lung lavage may greatly improve alveolar ventilation.

In cystic fibrosis, it would be expected that lung lavage would be of great benefit. However, one cannot recommend this as general practice, since experience with lavage in this disease is quite limited.

The clinical experience with lung lavage in the treatment of bronchiectasis, Goodpasture's syndrome, desquamative interstitial pneumonitis, chronic bronchitis, pneumonia, and inhalation of radioactive particles is not large enough to allow one to make recommendations as to the efficacy of this procedure in these disorders.

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Alpha$_1$-Antitrypsin Deficiency

AN ASSOCIATION between pulmonary emphysema and a deficiency of serum antitrypsin activity was first reported by Swedish investigators in 1963. This discovery has improved our understanding of the pathogenesis of pulmonary emphysema, and has resulted in the ability to detect individuals inherently predisposed to chronic obstructive lung disease. Alpha$_1$-antitrypsin is the major component of the alpha$_1$-globulin fraction of human serum, and it is inhibitory to a number of proteolytic enzymes including trypsin, elastase, chymotrypsin, and the leukocytic proteases. Being an acute phase reactant protein, alpha$_1$-antitrypsin has a fluctuating level that responds to infection, inflammation, estrogens and acute or chronic destructive tissue processes.

The proteolytic enzymes of leukocytes have been accused of causing the destructive process leading to pulmonary emphysema. In the advent of an intrapulmonary inflammatory reaction, leukocytes and other macrophages invade the area to engulf and digest cellular debris, but the lung parenchyma is protected from the digestive action of macrophagic proteases by the alpha$_1$-protease inhibitor. Persons with inherited deficiency of alpha$_1$-antitrypsin are unable to increase their level of antiprotease activity high enough to prevent the digestion of pulmonary alveoli, and emphysema results.

The inheritance pattern for antitrypsin deficiency involves two co-dominant genes. Abnormality of one of the two genes (heterozygosity) results in intermediate levels of antitrypsin activity, whereas the homozygous state results in a severe deficiency of this activity (approximately 10 percent of normal activity). It had originally been thought that only the severe homozygous deficiency state could result in pulmonary emphysema, but more recent findings have raised the very startling possibility that the heterozygous state may also predispose to chronic lung disease. If true, the number of affected persons would approximate 5 percent of the population. If only the homozygous condition predisposed to lung disease, the number of susceptible persons would be much less. Studies to date suggest that a heterozygous person is protected to a degree by his intermediate level of antitrypsin activity, but that continued or recurrent inflammation, as would occur in a heavy cigarette smoker, renders this limited protection inadequate.

The type of lung disease that occurs in these persons appears to be primarily a pure type of emphysema with predilection for the lung bases. This is in contradistinction to emphysema in persons with normal antitrypsin activity, where the upper lung fields seem to be primarily involved. In those with homozygous deficiency of antitrypsin activity, lung disease tends to develop at a younger age than in those with heterozygous antitrypsin deficiency or those with normal antitrypsin activity. It has been reported that a person in whom emphysema develops before age 50 has approximately a 50 percent chance of having either homozygous or heterozygous antitrypsin deficiency.

Current research is dealing with improved methods for detecting persons with intermediate levels of antitrypsin deficiency, and for confirming whether or not those with an intermediate deficiency are proclived to lung disease. Alpha$_1$-antitrypsin activity or concentration is measured either by immunodiffusion, using a specific antibody, or by an enzymatic assay of the trypsin inhibitory capacity of serum. Multiple alleles of the antitrypsin molecule have been detected by acid starch electrophoresis, and their relationship to lung disease is being studied.

Research is also being directed toward developing a therapeutic approach to this condition. It is known that the alpha$_1$-antitrypsin molecule is produced primarily by the liver. A liver transplant resulted in complete reversal of the antitrypsin abnormality in a child with the homozygous deficiency who was dying of infantile cirrhosis. This is an approach to therapy that may become more applicable in future years. Other modes of therapy being investigated involve methods for stimulating the body to produce more of the antitrypsin, or for replacing the deficient protein by parenteral means. An animal model is available for experimentation with the enzyme papain. Mammalian blood and tissue is incapable of inhibiting papain activity, and the instillation or inhalation of papain into the lungs can result in experimental emphysema. This animal model results in lung disease that resembles the pathologic changes found with antitrypsin deficiency, and it lends itself to experimentation with various drugs and hormones in attempts to prevent the destruction of lung tissue.

At the moment, no satisfactory therapeutic approach is available for correcting a deficiency of alpha$_1$-antitrypsin activity, and the main interest and concern of physicians should pertain to the detection of deficient persons and warning them against smoking or working in industry where they might be exposed to pulmonary irritants such as dusts or fumes. Pre-employment testing in certain industries should eventually become very rewarding.

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The Significance of Australia Antigen

AUSTRALIA ANTIGEN—Au(1) or Hepatitis B antigen (HBAg)—which was discovered by Blumberg in 1963, is a 200 Angstrom protein polysaccharide particle with a configuration resembling that of a virus. It has been found predominantly in the sera of patients with long incubation period post-transfusion hepatitis, but has also been detected in the sera of some patients with short incubation period hepatitis. The presence of this antigen, or its antibody or antigen-antibody complexes, has been found to have both diagnostic and prognostic significance.

A variety of assay systems are available for the detection of this particle, among them the radioimmunoassay, hemagglutination-inhibition and complement fixation tests which are highly sensitive. Immunodiffusion and immuno-osmo-electrophoresis are thought to be less sensitive, but are rapid, simple, and inexpensive. A rapid automated sensitive complement fixation assay has recently been described.

HBAg has many characteristics of a virus. It may be transmitted in blood products, orally, or transplacentally. Accordingly, it has been implicated in cases of post-transfusion, infectious, and neonatal hepatitis. HBAg may be found in 60 to 98 percent of patients with long incubation period, post-transfusion hepatitis; in 10 to 25 percent of patients with chronic active hepatitis; and it has recently been found among patients with primary biliary cirrhosis and in some patients with hepatoma.

The exclusion of HBAg-positive units of blood has reduced the frequency of post-transfusion hepatitis by at least 25 percent in some institutions. The presence of the antigen may aid in differentiating post-transfusion hepatitis from other forms of liver disease, such as drug-induced hepatitis. The persistence of HBAg for weeks or months may indicate the development of chronic liver disease. Anti-complementary complement fixation assays may indicate the presence of circulating antigen-antibody complexes which can be found in subacute or chronic hepatitis. Serial HBAg determinations among patients followed with serial liver biopsies have now revealed that some patients with HBAg-positive acute hepatitis may progress to HBAg chronic active hepatitis. Such patients may develop post-necrotic cirrhosis or occasionally may progress to primary biliary cirrhosis. Chronically ill patients such as those undergoing chronic hemodialysis or patients with immune deficiency states are particularly prone to HBAg-positive chronic liver disease.

Preliminary data suggest that inactivated HBAg may lead to the development of a hepatitis vaccine and that antibody to HBAg may confer some protection against the development of long incubation period hepatitis. These promising studies require confirmation.

The discovery of HBAg has led to new insight into the pathogenesis of acute and chronic liver disease. The HBAg assay offers important diagnostic and prognostic information to the clinician. Furthermore, exclusion of HBAg positive blood donors may significantly reduce the frequency of post-transfusion hepatitis.

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Some Effects of Ischemia on Heart Muscle

MYOCARDIAL ISCHEMIA produces a rapid loss of contractile strength. Fogelman et al demonstrated that diastolic motion of the posterior ventricular wall is impaired during angina pectoris. This abnormality was reversed by nitroglycerin and is consistent with evidence for impaired relaxation of ischemic muscle observed in the animal laboratory. Impaired relaxation can contribute to decreased distensibility of the ischemic left ventricle during myocardial infarction and thereby explain the high left ventricular filling pressures seen in some patients with acute infarctions despite normal sized cardiac silhouettes. Digitalis can improve myocardial function early after acute myocardial infarction but without significant increase in cardiac output. The failure of digitalis to alter ventricular distensibility may account for failure of the drug to significantly improve cardiac function in some infarct patients, particularly those with small heart size.

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The Use of Sulfonylureas in the Treatment of Adult Onset Diabetes

RESULTS OF THE University Group Diabetes Program (UGDP) study revealed an increased cardiovascular mortality and no clear-cut reduction in vascular complications in diabetics treated with tolbutamide (Orinase®). This led the Federal Drug Administration to advise against the use of sulfonylureas in general, except in very special circumstances. However, other publications do not confirm these observations and a large body of practicing diabetologists, I among them, feel that when sulfonylureas can be proved to be effective in lowering blood sugar, their use is actually beneficial and indicated. I institute a strict diet, attempt weight reduction at all cost, and often achieve normalization of the fasting and two-hour postprandial blood sugar. Only if this fails and the patient is not ketoacidosis-prone are sulfonylureas given for up to two weeks.

After this period, a two-hour postprandial blood sugar, after the patient's usual breakfast, should fall within 10 mg per 100 ml of the fasting level. Failing to achieve postprandial blood sugar control, I start insulin, since 40 percent of patients on sulfonylureas may show secondary failure within a five-year period of treatment.

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Protamine Sulfate Test—Its Role in Differentiating Disseminated Intravascular Clotting from Primary Fibrinolysis

DISSEMINATED INTRAVASCULAR clotting (DIC) and primary fibrinolysis are disorders in coagulation associated with a number of common pathologic conditions. The therapy for each of these conditions is specific. Therefore, erring by treating disseminated intravascular clotting with epsilon amino caproic acid or primary fibrinolysis with heparin may lead to intensification of the pathologic process with subsequent bleeding or thrombosis. Laboratory studies such as the partial thromboplastin time, Quick prothrombin time, thrombin time, and fibrinogen titer only detect reductions in the quantity of plasma clotting factors and as a result are not specific for either coagulopathy.

The plasma protamine sulfate test, using 0.1 percent protamine sulfate in plasma at 37°C, specifically reveals the presence of soluble fibrin. Soluble fibrin can only result from the action of thrombin on fibrinogen and in disseminated intravascular clotting thrombin, not plasmin, is the principal enzyme acting on fibrinogen.

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The Significance of Triiodothyronine

TRIIODOTHYRONINE (T-3) once considered of only secondary importance compared to thyroxine (T-4), now appears responsible for the majority of the effects of thyroid hormones in normal subjects. A significant proportion, approximately one-third, of the T-4 metabolized daily is converted to T-3, and T-3 is three to four times as potent as T-4. These considerations have, in fact, raised a question whether T-4 has any intrinsic hormonal activity by itself or whether it serves merely as a "prohormone" for the hormone, T-3. The issue has not been settled fully as yet, although analysis of certain clinical situations does favor some direct hormonal role of T-4.

T-3 circulates in human serum in a concentration approximately one-seventieth that of T-4. Recent studies indicate that the T-4 to T-3 ratio in thyroglobulin is normally about 19 to 1 rather than 4 to 1 as surmised previously. Assuming that T-4 and T-3 are secreted in the same proportion that they exist in thyroglobulin, it can be calculated that only a minor fraction (approximately 20 to 30 percent) of circulating T-3 originates from thyroidal secretion. The remaining serum T-3 would appear to derive from extrathyroidal sources. Serum T-3 is normal in hypothyroid patients maintained on synthetic T-4 in a dose sufficient to increase serum T-4 concentration to normal. This finding strengthens the consideration that circulating T-3 derives mainly from extrathyroidal conversion of T-4.

The ratio of concentrations of serum T-3 to T-4 is considerably above normal in patients with Graves' disease. Therefore, the measurement of serum T-3, now available commercially, is even more helpful in the diagnosis of hyperthyroidism than is T-4. The entity of "T-3-thyrotoxicosis," where hypermetabolism is due to elevated serum T-3 in the face of normal serum T-4, is now established. It may be suspected in clinically hyperthyroid patients with diffuse goiter or in those with a solitary or multiple nodules in the thyroid gland. On the other hand, measurement of serum T-3 is a less definitive test for diagnosis of hypothyroidism, where measurements of serum T-4 and thyroid stimulating hormone (TSH) are more helpful.

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Human Tumor Viruses

IN RECENT YEARS viruses have been found in association with several human tumors. In no case, however, has a virus yet been shown to be the cause of human malignant disease. The prospect that human tumor viruses do exist and that methods may be available to identify and study them has been suggested in extensive experimental work with tumor viruses in lower animals. These studies have demonstrated remarkable similarities in the physical characteristics and biological behavior of tumor viruses from species to species. Among the known tumor viruses are the deoxyribonucleic acid (DNA) herpes viruses, such as the lymphoma-producing Marek's disease virus of chickens, and the ribonucleic acid (RNA) viruses with lipid-containing envelopes which cause mammary adenocarcinoma in mice and leukemias and lymphomas in chickens, mice, cats and probably other species.

One example of a virus found in association with human cancer is Epstein-Barr (EB) virus, a herpes virus. Patients with Burkitt's lymphoma and carcinoma of the postnasal space have very high titers of EB virus antibody in their blood, and EB virus has been found regularly in tissue culture cell lines established from lymphoma tissue. Although these tumors are quite rare, serological evidence indicates that EB virus infection of humans is very common. At least some acute infections in young adults appear to be associated with infectious mononucleosis and many infections, particularly in infants and children, are probably clinically inapparent and may persist for years. Recently EB virus antibody titers have been reported to occur more frequently and in higher titer than in the general population in several other diseases. These are Boeck's sarcoid, systemic lupus erythematosus, Hodgkin's disease and lymphocytic leukemia. It will undoubtedly be difficult to determine whether EB virus is etiologically related to any of these disorders or whether patients with these lymphoproliferative disorders are merely more susceptible to EB virus infection or activation of latent infection. Establishing convincing evidence that EB virus causes any neoplastic disease will be difficult because, like other herpes viruses, EB virus appears to be ubiquitous in the population and to persist in patients for many years; and it does not appear to readily infect experimental animals.

Another tumor virus candidate found in humans is a recently discovered particle in human breast-milk. This particle has the same characteristics and unique morphologic features as the Bittner mammary tumor virus found in the breast-milk of mice. The occurrence of the human particles in the milk of American women has been reported to be highly correlated with family history of breast cancer, as is the Bittner virus in mice. Although no direct tests have been made to determine whether the two viruses are antigenically related, serum from women who have had breast cancer has been reported to block the tumorigenicity of the murine virus, suggesting the presence of antibody in breast cancer patients capable of neutralizing murine mammary tumor virus. The virus particles from human milk have also been shown to contain the RNA-dependent DNA polymerase enzyme recently shown to be present in all known RNA tumor viruses. The similarities of this human virus to the Bittner virus of mice make it a suspicious candidate for a human tumor virus. The kinds of evidence that will be needed to prove this will include demonstration of infectious virus or a virus determined antigen or nucleic acid in cells of human tumors, evidence for infection and tumor induction by the virus in experimental animals or cells in culture, and protection of humans by vaccination with a viral vaccine. Obviously some of these will not be easily or quickly done.

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EDITORIAL

Diabetes Mellitus

DIABETES MELLITUS is an enigma, best (yet poorly) described as a constellation of morphologic and metabolic sequelae to an underlying disorder which, itself, is almost always manifested by abnormalities in insulin and carbohydrate homeostasis. It is certainly inherited, but influenced strongly by environment, being more frequent in populations with caloric affluence and decreasing during times of deprivation. As discussed by Rimoin in the Specialty Conference which appears elsewhere in these pages, the precise mode of inheritance is complicated. Tattersall and Pyke,[1] in a recent and most provocative discussion of concordance for diabetes in identical twins, have noted environment to play a greater role beneath the age of 40, and, over 40, heredity the more important role. At first this appears to be a paradox for a supposedly inherited disease, but with the recent demonstrations of Beta cytotropic viruses causing diabetes in experimental animals and possibly in man[2,3] the paradox may be partially resolved, as follows.

The natural history of the Beta cell in man, let alone in experimental animals, is poorly understood. Do we have the same Beta cells given us at birth? Probably not. As we do with liver cells and possibly those of the exocrine pancreas and other endodermally derived tissues, we are always replacing old Beta cells with new ones. What controls this process? We know the cells arise by mitosis from already formed Beta cells,[4] but we know little of the initial stimulus to cell division, what it is or wherefrom it arises. It is even conceivable that diabetes may result from lack of the signal itself. This problem is analogous to what controls the mass of the liver and its regeneration after disease or partial resection.

As Bray notes in the Specialty Conference, obesity is associated with higher insulin levels, and both in experimental animals and man, with Beta cell hyperplasia. Thus "normals" can probably augment their insulin-secreting capacity in the presence of the increased needs induced by the peripheral insulin resistance of the obese state. What causes this resistance is another challenging problem awaiting solution. That the sequence can be simulated by promoting obesity in otherwise normal people has been shown by the classical studies of Sims and colleagues in Vermont, as discussed by Bray, in which force-feeding of human volunteers induced probable Beta cell hyperplasia, as manifested by higher basal and stimulated insulin levels; although morphologic confirmation is obviously lacking.

Why doesn't the obese maturity-onset type of diabetic increase his insulin reserve even more to overcome the diabetes, perhaps by even a greater degree of hyperplasia? It is tempting to speculate that the primary lesion may simply be a deficiency in Beta cell reproductivity. In youth a virus might cause loss of most of the Beta cells, and the inherited limited regenerative capacity may be associated with a temporary remission, followed by relapse and eventually by loss of all endogenous insulin production. The capacity to measure endogenous insulin production in insulin-treated juvenile diabetics by the detection of a byproduct (connecting peptide) in peripheral blood by Steiner's group[5] has confirmed this sequence of events. In the adult, the programmed Beta cell premature senescence may result in diabetes at age 70 or 80, but if in an obese individual, it may result in the mild maturity-onset type of diabetes at an earlier age, due to the increased insulin needs of the obese.

Although juvenile diabetics tend to breed juvenile diabetics as contrasted with maturity-onset diabetics (M. Gottlieb, unpublished, 1973), the association of the two types of diabetes with each other in a given family is much greater than the association of either type with diabetes in the general population. Thus the same heredity basis is common to both ends of the diabetes spectrum.

Goldstein et al[6] reported that fibroblasts from young diabetics exhibit an earlier senescence in tissue culture than do fibroblasts taken from older, normal, non-diabetic persons, and this same decreased *in vitro* longevity is shown by fibroblasts from offspring of two diabetic parents. The Beta cells may therefore be the Achilles heel of a decreased generalized mitotic potential; but this, at the moment, is very speculative. The numerous other genetic diseases described by Rimoin, which are associated with diabetes, support the heterodisperse nature of the inherited defect, and, from a biochemical basis, demonstrate that any number of mutations resulting in a broad array of other inherited abnormalities may be associated with diabetes. This again suggests the Beta cell is more "fragile" or limited as far as its regenerative capacity is concerned.

One may ask why the Beta cell has been selected out as the weak link—why not the thyroid cell, or that in the adrenal cortex? The hair follicles in many males and some females and the ovarian cortex in all females also undergo an earlier senescence, but these are relatively dispensable tissues as compared with the Beta cell. The riddle cannot be answered as yet, unless mild diabetes might have offered at one time some degree of selective advantage.[7]

Finally, is the entire constellation, mentioned in the first sentence of this editorial, simply a result of the Beta cell deficiency? Many investigators feel it is, and there are recently published biochemical data in support,[8] but until long-term insulin and carbohydrate homeostasis is maintained by an artificial pancreas, or by successful long-term transplantation of Beta cells or even by rejuvenation of Beta cells remaining in the diabetic (all these possibilities are now being put to experimental test[9]), one cannot answer with confidence. The vast majority of those in the field, however, act as if the complications result from the disturbed insulin-carbohydrate homeostasis, and treat the disease accordingly.

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Some Caveats for the FDA

Recent decisions by the United States Supreme Court appear to give the Food and Drug Administration (FDA) very significant powers to decide what drugs and medicines can be marketed in the United States. A federal bureau will now have real power to decide which drugs a physician may prescribe for what purpose in caring for his patients, and those which he may not. This is a very considerable power which strikes very close to home for physicians and patients alike. And unless it is exercised wisely and with an understanding of human nature and human needs and the realities of clinical medicine, it may not be very popular.

The Supreme Court opinion itself, written by Associate Justice William O. Douglas, traces the growth of FDA authority and responsibility since 1906. The 1906 Food and Drug Act provided for criminal sanctions and seizure for condemnation of drugs found to be *adulterated* or *misbranded*. The Food, Drug and Cosmetic Act of 1938 established a system of pre-marketing clearance for drugs, the emphasis being upon the *safety* of the drug. The 1962 amendment of the 1938 Act directed the FDA to refuse approval of a new drug application if "substantial evidence" that the drug is *effective* for its intended use is lacking. The 1973 decisions of the Court now give the FDA the power to force drugs it deems to be ineffective off the market, to issue strict rules governing product effectiveness, to deny hearings to manufacturers on contested actions, and to proceed against entire product classes rather than individual drugs. These are significant and substantial powers.

While the distinction between a drug that is adulterated or misbranded and one that is not is clear enough, this clarity of distinction blurs somewhat when it comes to deciding upon safety and effectiveness. There are very few drugs that are entirely safe and always effective. There is nearly always some element of danger in the administration of any drug. Safety is therefore a matter of degree, and the degree is often a matter of conjecture since it depends upon effects of the drug which may not be known and upon the reaction or response of an individual patient which is never entirely predictable; and it is paradoxically true that the scientific proof of the effectiveness of a given drug usually follows rather than precedes clinical experience with it, and this proof may take years to establish. In practice, both the safety and effectiveness of a drug in a given circumstance are apt to be considered in terms of probabilities. The size of the risk to be taken in terms of safety and probable effectiveness is a matter to be decided by the physician with the informed consent of the patient. In serious or desperate situations, quite sizable risks may be opted by physicians and patients alike, and if these options should become too restricted by bureaucratically imposed criteria of safety and effectiveness for the intended use, some patients who are most in need may be deprived of the chance of relief or cure which should be their right. It is suggested that judgment, a judgment that is in many ways related and similar to clinical judgment, should be exercised by the FDA in determining what risks are acceptable in the marketing of drugs.

Human nature and human needs will affect both the actions taken by the FDA and the response to these actions on the part of physicians, patients and the public; and it is possible that the restraints imposed by the Supreme Court on the use of court actions to stay or reverse any FDA decisions may intensify some of these responses as time goes by. A few caveats are offered:

- There will be an understandable and very human temptation for the FDA bureaucracy, in order to protect itself, to err in the direction of prohibiting the marketing of a drug if there is any chance that it may be unsafe or ineffective. Not only can this deprive Americans of drugs which can be used with benefit, and are being so used elsewhere in this world, it can be a serious deterrent to progress in drug development in this nation. This of course would be a disservice to the public which is to be served.
- Human nature is such that many persons believe in drugs and rely upon them for relief of real or fancied ailments. There is some evidence that Americans are particularly drug-oriented in this sense. It is suggested that a case can be made for permitting the sale of some relatively harmless and relatively ineffective drugs to satisfy these human needs.
- Simply ordering a drug off the market does not assure its disappearance. Experience has shown that if there is a human need or a strong desire for a drug, the American people are capable of developing alternative means of supply which can make mockery of both the law and its enforcement.

It is clear that much will depend upon the wisdom and statesmanship with which the new FDA powers are used. The aim, to rid the market of unsafe and ineffective drugs, is laudable and to be supported. We suggest that success will not come easily for many reasons, some of which have been given here. We suggest that success will be more likely if clinical realities and human needs and human nature are all taken into account when the decisions are made. And we further suggest that the FDA involve all those who should be involved—that is, practicing physicians, consumers, and, of course, the pharmaceutical industry—in its decision-making processes.

—MSMW

A Case for "Backlash"

In his article "Backlash—The Case for American Medicine," which appears elsewhere in this issue, Francis D. Moore borrows part of his title from Schwartz's well known book,[1] and then proceeds to carry the case for American medicine considerably further. In his address to the graduating class of one of California's medical schools, Dr. Moore forthrightly considers the gamut of recent attacks on American medicine and some of the reasons for them, and provides much valuable information and formidable logic for what he suggests is an overdue rejoinder from American medicine against these attacks. In particular he deplores political polarization where medicine and health care are concerned and emphasizes that usually there are worthwhile values in both the opposing views. He points out that as scientists we learn to see both sides of problems and urges us as physician politicians to persuade others to see likewise.

There is much of positive thought in Dr. Moore's article and it is well worth careful perusal by all physicians, and especially by those who feel that the time has come for more of a rebuttal against the recent and current rash of attacks on American medicine. Dr. Moore presents a considerable amount of ammunition for such a rebuttal.

—MSMW

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CASE REPORTS

Refer to: Ambrus L, Papatheodorou C: Trauma and lumbar disc herniation in childhood. Calif Med 119:66-68, Oct 1973

Trauma and Lumbar Disc Herniation in Childhood

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Low back pain in general and lumbar disc herniation in particular are rare occurrences in childhood. In both conditions the signs are more important than the symptoms.

During a one-year period, we observed and treated 500 patients with low back pain. Only ten of them (2 percent) were children. One 14-year-old began to have low back pain with radiation to the lower extremities after a football injury. Conservative treatment was tried for six weeks but signs persisted. A lumbar myelogram showed a large central herniation of the fourth lumbar disc. Lumbar laminectomy with removal of the herniated disc was performed. The recovery was uneventful.

In a review of the literature several case reports of lumbar disc herniation in children were found. Compared with the incidence in adults, lumbar disc herniation in childhood is still a rarity.

It could pose a difficult problem, for only a few physicians have even limited experience with this condition in children. The first report of operation in such a patient was Wahren's[1] account of the treatment of a 12-year-old child in 1946. Since that time several single case reports and more extended reviews have been published.[2-15] The usual lumbar disc herniation results from aggravating trauma to a previously existing abnormally weak area in the anulus fibrosus. Most herniations occur posteriorly, where the anulus is anatomically thinnest and weakest. As in adults, trauma plays an important role in herniation, but in children it generally is not caused by lifting as it usually is in adults, but rather by injury in competitive athletics.

Report of a Case

A 14-year-old high school student injured his back while playing football. He described the accident as follows:

"We had practiced in full gear. We went through our drills, consisting of rolls, running and kicking high, moving from side to side, then falling on our guts, then jumping to block a pass. Then we had a scrimmage, we were beating the tar out of each other. I fell on a fumble and so did everyone else. I felt somebody's knee in my back and my back became sore."

Shortly after the injury the patient was seen in the Emergency Room because of complaint of pain in the back. On x-ray examination of the spine, the antero-posterior films showed levoscoliosis but no other abnormalities appeared on the lateral and oblique views. The diagnostic impression of the examining physician was "muscle strain." The patient was advised to follow a home program of bed-rest and local application of heat. When his condition did not improve after three days of home treatment, he was referred to the Department of Physical Medicine for further evaluation and treatment.

Although he felt no pain in a recumbent position with slightly flexed knees, the patient complained of pain in the lower back, with radiation to his gluteal area while in a standing position. He spoke of a vague numbness and "funny" feeling over the soles and the outer sides of his feet and calves.

On physical examination the patient, who was 6 feet 1 inch tall, weighed 220 pounds and was well-developed, was observed to stand with slightly flexed knees and there was loss of lumbar lordosis, a forward list and slight levoscoliosis. The range of motion of the lumbar spine was severely limited and spasm of the paravertebral muscles in the lumbar region was evident. Tenderness was elic-

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ited over the entire lumbar spine on light pressure. The straight leg raising was 25 to 30 degrees bilaterally with positive Lasègue's signs. Deep tendon reflexes at the knees and ankles were 3 plus. Sensation to pin-prick was normal. Definite muscle weakness of the great toe extensor was noted bilaterally.

The patient was advised to continue conservative treatment consisting of bed-rest and application of heat. After a short interval the patient was admitted to hospital. Conservative treatment of complete bed-rest with 20 pound pelvic traction in the semi-Fowler position was continued for eight additional days. The patient denied any symptoms during bed-rest but the signs persisted. Electromyographic examination was performed 18 days after injury. Decreased voluntary motor units were seen, but no fibrillation potentials or positive sharp waves were noted. Nerve conduction velocities of both peroneal nerves were within normal limits. A lumbar myelogram was done on the ninth day in hospital. A central disc herniation between the fourth and fifth lumbar vertebrae, with almost complete obstruction, was seen on anteroposterior films (Figure 1). Spinal fluid total protein was elevated to 110 mg per 100 ml. Routine laboratory data were unremarkable. Bilateral lumbar laminectomy at the fourth to fifth interspace showed a large herniation of the fourth lumbar disc and a 5 cm fibrocartilage was removed.

The post-surgical course was uneventful. At the time of discharge, the patient was able to walk erect and without difficulty. Six months later he was asymptomatic, showed no muscle weakness and could perform all normal physical activities.

Discussion

The exact incidence of lumbar disc herniation in children is unknown. Several extensive reviews of surgically treated cases of children and teenagers mention an incidence of zero to 3.2 percent (Table 1).

According to O'Connell's[7] definition, childhood extends from birth to puberty—12 years in girls and 14 years in boys. Webb[4] chooses to end the period of childhood at the sixteenth birthday. The age of the patient in the present case was 14, by Webb's definition a child.

Bradford and Garcia[12,13] reported 36 patients whose symptoms began before or at age 16. In their opinion, lumbar disc herniation after this age is common enough that it does not cause diagnostic or therapeutic difficulties.

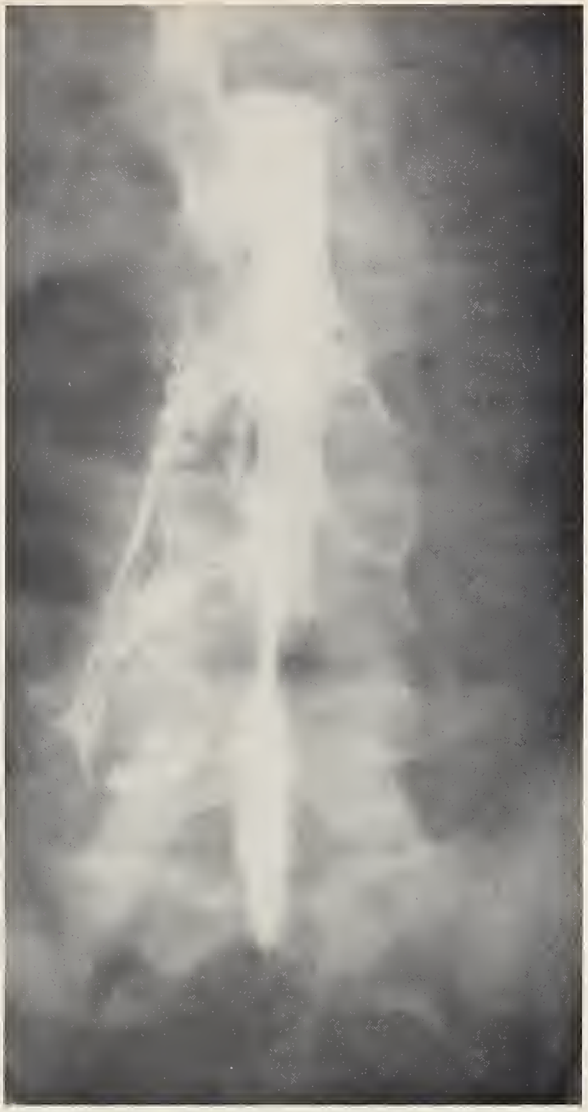

Figure 1.—Postero-anterior upright radiograph during lumbar myelography shows a bilateral extradural compression of subarachnoid space and incomplete filling of the root sleeves at the L4-L5 interspace. There was incidental extradural extravasation of contrast media around aortic vessels.

TABLE 1.—*Incidence of Lumbar Disc Herniation in Children and Teenagers (Surgically Treated Cases)*

	Number of Patients	*Age (years)*	*Incidence of Disc Herniation (percent)*
Gurdjian et al. (1961)	1,176	<17	0.0
Webb et al. (1954)	6,500	<17	0.18
Rugtveit (1966)	840	11-17	0.8
O'Connell (1960)	1,200	<16	1.3
Epstein and Lavine (1964) .	560	15-19	1.8
Raff (1959)	905	10-19	2.0
Love (1947)	1,218	10-19	2.1
Knuttson and Wiberg (1958)	267	10-19	3.2

Trauma plays an important role in lumbar disc herniation.[1,3,4,7-9,11,13,14] Bradford and Garcia in their latest report[13] found that in 19 of 36 cases there was definite history of trauma—major trauma in ten cases and strains of a twisting type in nine. O'Connell[7] found an even higher incidence of trauma: 66 percent in 38 patients. Epstein[9] in a report of ten cases noted that seven patients had a history of direct trauma, two claimed occupational stress and only one could not recall any trauma or stress.

Day[11] said that lumbar disc herniation in children does not result from episodes of lifting as is customary in adults, but rather from involvement in competitive athletics, such as baseball, basketball and football. Trauma in this age group plays a more important precipitating role in adult groups. In adults, preexisting degenerative alterations in the disc render this structure susceptible to herniation.

Reports on the incidence of history of trauma vary widely: Gurdjian[16] reported it at 35 percent and Raaf[6] at 70 percent.

The absence of significant degenerative alteration in children's discs would help explain the importance of trauma. In rare cases, degeneration can be found in this age group.[9] Degenerated fibrocartilage was found in all three patients reported by Rand and Rand.[17] Degenerative changes were found in ten patients and normal discs in 17 patients in the Bradford and Garcia[13] report.

There are different opinions regarding sex distribution. Epstein and Lavine[9] found an equal distribution between males and females, Love[2] a slightly greater incidence in males. Jones[18] expressed belief that disc herniation predominates two to one in females, and he noted also that children with disc disease are usually large for their age.

The two youngest children with disc herniation, aged 9, were reported by Ford[19] and Janecki.[15]

There is considerable controversy as to whether signs or symptoms are more significant in juveniles. Rugtveit[10] and Day[11] noted that complaints are minimal but physical signs are obvious. O'Connell[7] felt that objective findings dominate in children as compared with adults but neurological findings are rare. On the other hand, Epstein,[9] Key,[3] and Webb[4] said that clinical manifestations do not differ from those of adults. It is possible that children do not verbalize as well as adults.

Almost all herniation is between the fourth and fifth lumbar and the fifth lumbar and first sacral interspaces. Bradford and Garcia[13] found 16 cases in which it was between L4 and L5 and 20 between L5 and S1. O'Connell[7] noted seven cases between L4 and L5 and 15 between L5 and S1.

Conservative treatment is stressed by most of the observers. Only if symptoms and signs persist after an adequate period of conservative treatment should lumbar myelogram and laminectomy be considered. Janecki et al,[15] by comparing children and teenagers with adults, found that operation produces a better overall result in teenagers and that a higher proportion of them can return to former activity, and sooner, than adults. Janecki[15] and Day[11] advise that the excellent results of operations in this age group should encourage active surgical treatment in cases refractory to conservative measures.

Summary

A 14-year-old boy injured his back while playing football. After an adequate period of conservative treatment, a lumbar myelogram was done which showed central disc herniation at the fourth to fifth lumbar interspace. Lumbar laminectomy and removal of the herniated disc was performed. The recovery was uneventful.

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Refer to: Sadler RB, Fitzgerald G: Interruption of the inferior vena cava with azygos continuation and pulmonary embolus. Calif Med 119:69-72, Oct 1973

Interruption of the Inferior Vena Cava with Azygos Continuation and Pulmonary Embolus

RUSSELL B. SADLER, MD
San Bernardino

GARRY FITZGERALD, MD
Houston

THIS COMMUNICATION CONCERNS a case of partial abdominal situs inversus[1,2] and interruption of the inferior vena cava with azygos continuation, in which pulmonary embolus was the presenting and principal feature. No causal relationship is known. In the many cases of this rare vascular anomaly that have been reported, some of the patients have had normal hearts,[3,4] some have had various cardiac malformations,[3,5,6] and others acquired heart disease,[7] polysplenia,[1,2,8] and asplenia (Ivemark syndrome),[9] but we are not aware of any case in which this condition has been associated with pulmonary emboli.

Report of a Case

A 20-year-old white man was well until June 1971, when he began to have exertional dyspnea, non-productive cough and substernal pleuritic pain. He was treated by his physician with antibiotics, initially penicillin and then tetracycline. He did poorly, lost approximately 20 pounds between May and September 1971, and had recurring chest symptoms.

On 27 September 1971 he was admitted to the San Bernardino County General Hospital with exacerbation of the chest symptoms but no hemoptysis. The patient had no history of trauma, recent surgical operation, leg swelling or drug abuse. Breath sounds were diminished and percussion dullness was present over the lower right lung. The second pulmonic sound was greater than the second aortic. No murmurs or rubs were heard in the chest.

Roentgenograms of the chest (Figure 1) showed a right middle lobe infiltrate and situs inversus of the abdomen.

Blood gases at this time were pO_2 46.9, pCO_2 28.5, pH 7.41, bicarbonate 18, base excess minus 5, SO_3 83. The electrocardiogram showed right axis deviation, inverted T-waves in V-1 through V-3, and sinus tachycardia.

A lung scan (Figure 2) showed a striking and extensive loss of vascular perfusion of the left lung and several perfusion defects in the right lung. Pulmonary arteriography (Figure 3) showed

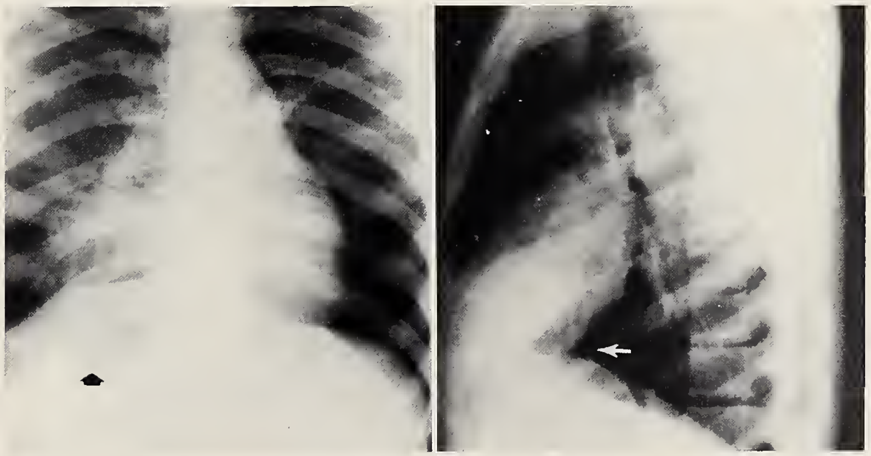


Figure 1.—Frontal and lateral views show a right middle lobe infiltrate. Note in the frontal film the right-sided position of the gastric air bubble (arrow) with normal aortic and cardiac situs. In the lateral view no inferior vena cava shadow can be identified (arrow).[17]

From the San Bernardino County General Hospital, San Bernardino. At the time this article was submitted, Dr. Sadler was Associate Radiologist, San Bernardino County General Hospital; Mr. Fitzgerald was a 4th year medical student, class of 1973, University of Guadalajara.

Submitted December 7, 1972.

Reprint requests to: R. B. Sadler, MD, Department of Radiology, San Bernardino County General Hospital, 780 East Gilbert Street, San Bernardino, CA 92404.

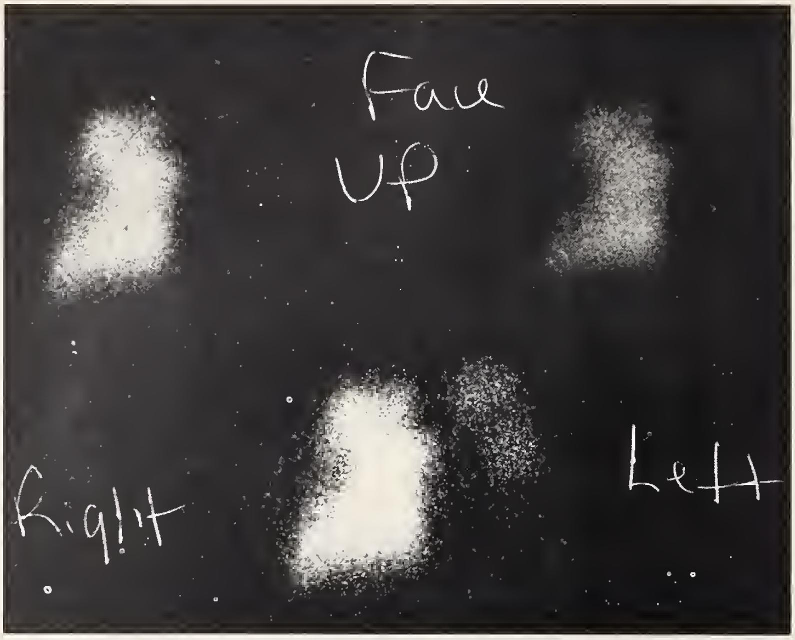
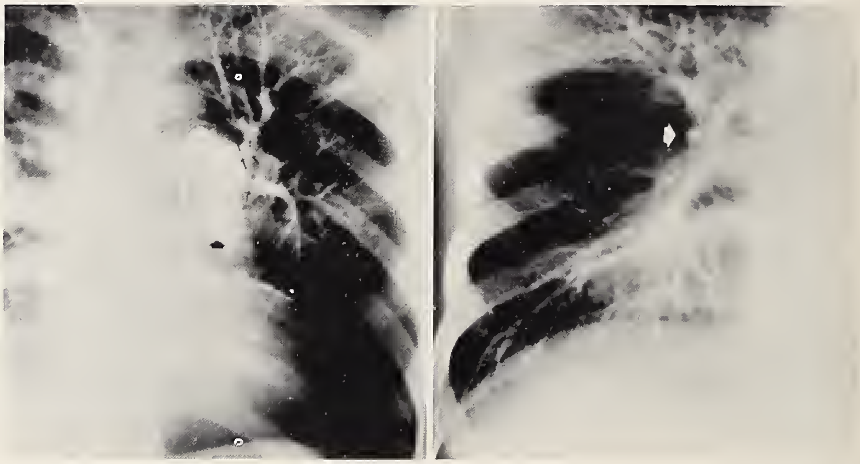


Figure 2 — An ^{131}I macro-aggregate radioisotope scintiscan made with the Anger Gamma camera shows striking deficiency of vascular perfusion in the major portion of the left lung and perfusion defects in the right lung.

Figure 3.—Left pulmonary arteriogram (**left** frame) documents a large clot almost occluding the major descending branch of the left pulmonary artery (large arrow) and extending distally along the vessel and its branches. Other occlusive lesions are present in the smaller branch vessels (smaller arrows). The right pulmonary arteriogram (**right** frame) shows large central avascular area with occlusive lesion (arrow).



a large clot in the major descending branch of the left pulmonary artery and several smaller clots in branches of both right and left pulmonary arteries.

Pulmonary embolus was diagnosed and heparin was administered. The patient did well clinically and was discharged, receiving coumadin therapy, 31 October 1971. A roentgen study of the stomach and mesentric small bowel before the time of discharge confirmed and clarified the abdominal situs inversus (Figure 4).

The patient did well until 9 November 1971, when he was readmitted to the hospital with left pleuritic chest pain, chills and fever of 104°F. Rales were heard over the lower left lung and the second pulmonic sound was accentuated. Blood gases were pO_2 81.5, pCO_2 34, pH 7.47. Sputum yielded Gram-positive diplococci and a lung scan showed no change from that of 21 October 1971.

The pneumonia was treated with antibiotics—erythromycin initially, then penicillin. There had been difficulty in stabilizing the anticoagulant therapy throughout the entire course of treatment, and at this time there were clinical signs of peritoneal or retroperitoneal bleeding. This was controlled with 5 mg of aquamephyton and fresh frozen plasma. The prothrombin time and partial thromboplastin time became normal and the symptoms subsided. The pneumonia cleared.

Inferior vena cavography showed interruption of the inferior vena cava with azygos continuation to the superior vena cava. The inferior vena cava was narrowed and angulated at its junction with

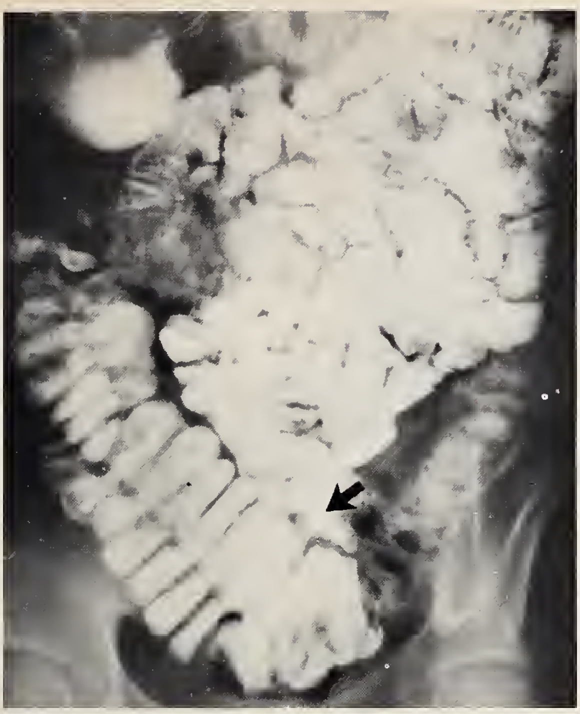


Figure 4.—Delayed film following upper gastrointestinal study shows the stomach on the right with normal distribution of small bowel. The ileo-cecal junction is displaced toward the midline (arrow) but retains normal left to right orientation.

the anomalous azygos vein, in which multiple clots were present (Figures 5 and 6).

The patient was discharged 27 November 1971 in good condition, receiving coumadin anticoagulation therapy.

Discussion

Brodelius et al[5] traced the original anatomic description of interrupted inferior vena cava with azygos continuation and situs abdominus inversus to an autopsy finding by Dorsch in 1858.[10] Many observers have since further elucidated this rare condition,[3,11,12] and it has been reported with increasing frequency since the advent of angiography. Many investigators have described the embryology of this malformation.[3,6,13-15]

The most important plain film finding is the discordant relationship of the gastric air bubble to the aortic arch and left ventricular shadow in the frontal films of the chest.

Elliott et al[1] and Elliott and Schiebler[2] analyzed malformations of this general type and proposed a nomenclature which simplifies the subject and relates the various forms of situs to specific cardiac and vascular malformations.

Other helpful roentgen signs have been described[2,4,16-18] and recent articles have dealt with the roentgen diagnosis of polysplenia, a frequent component of this anomalous complex.[19,20]

The major significance in recognizing this anomaly is its frequent association with cardiac malformations.[3,8] Where this is the case, right heart catherization and angiocardiography should be carried out from the veins of the upper extremity or neck via the superior vena cava rather than through the frequently used lower limb approaches.[3,7] This condition also requires special considerations when the heart-lung machine is used during surgical correction of the cardiac anomalies.[9]

Although our patient had no detectable heart lesion, the recurrent pulmonary emboli presented another important reason that the malformation be identified. Ligation or clipping of the inferior vena cava, used effectively in selected patients with recurrent pulmonary emboli,[21-23] would probably have been lethal in this patient.[3,24]

No relationship between this venous malforma-

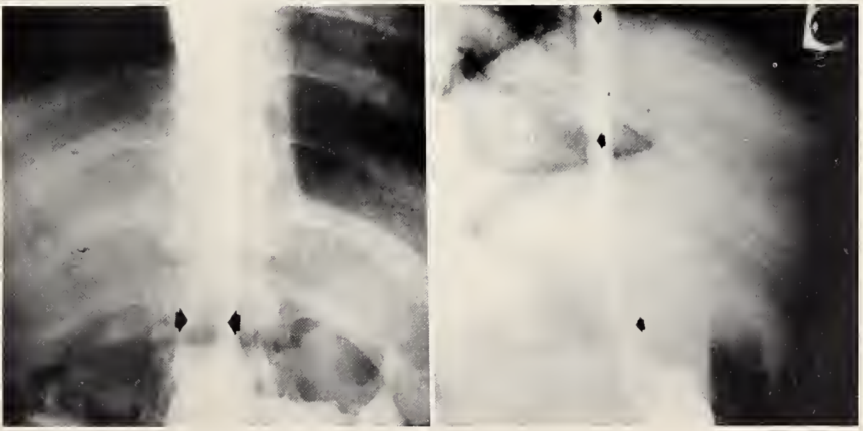


Figure 5. — Left, an inferior vena cavogram shows interruption of inferior vena cava in frontal view, with azygos continuation. The lucent shadow in the opacified anomalous azygos vein (between arrows) persisted, representing a large clot. Smaller clots, more cephalad in the azygos, were readily appreciated on the original films. The lateral view at **right**, made simultaneously, shows the abrupt change in course and calibre of the lumen at the anomalous venous connection. Some of the more obvious clots are marked with arrows.

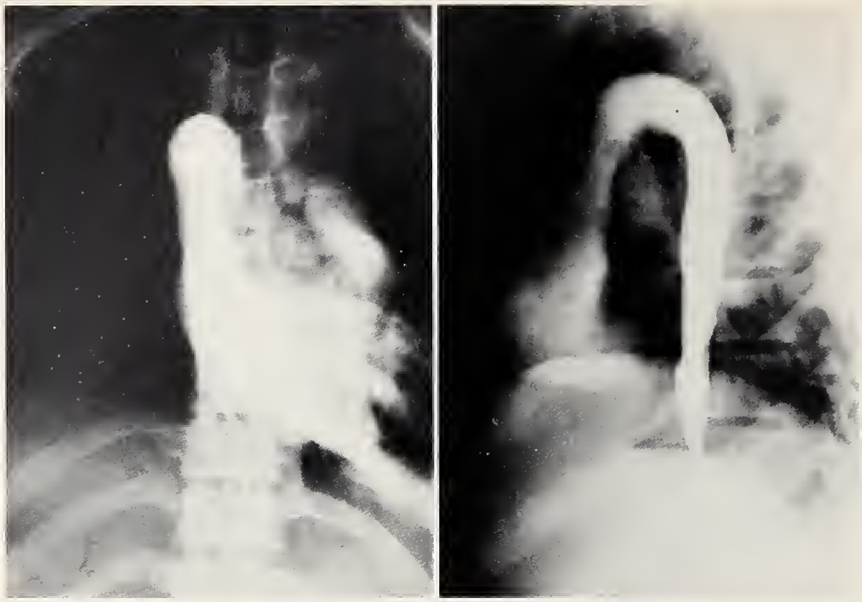


Figure 6.—In the frontal view, **left,** with the catheter in a higher position the azygos was observed to ascend to the right of the spine. This film shows the right heart and pulmonary trunk opacified. In the lateral view, **right,** the classical "candy-cane" configuration[3] of the opacified azygos vein is seen describing a sharp curve as it ascends ventrad over the right main stem bronchus to enter the superior vena cava. The right atrium is opacified.

tion and recurrent emboli is known, and no cases similar to this were found in the literature. If abnormal eddy currents were induced in the inferior vena cava-azygos continuation sufficient to cause thrombi, it would be expected that other patients with these findings would have been reported.

Summary

A 20-year-old man presenting with pulmonary emboli was found to have partial abdominal situs inversus and interruption of the inferior vena cava with azygos continuation. There were extensive emboli and thrombi in pulmonary arteries bilaterally, and in the azygos continuation of the inferior vena cava. None of the usual predisposing factors for pulmonary emboli were present. No reports of pulmonary emboli in patients with this vascular anomaly were found in the literature, and no relationship between the two conditions is known.

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LETTERS *to the Editor*

Vitamin E Fatigue?

To the Editor: Dr. Harold M. Cohen's interesting letter appearing recently in California Medicine [Calif Med 119:72, July 1973] has just been brought to my attention and I hasten to make what comment I can on it.

We have never known vitamin E to produce fatigue such as Dr. Cohen describes. Indeed, it is used very widely all over the world by athletes and race horse owners to *increase* energy. There are a good many references in the literature to attest to the accuracy of this observation, one of the most outstanding being General Nayar's observations on mountain troops in the Himalayas who were given large doses of vitamin E.

It would be a singular thing if eating what amounts to a food would *decrease* one's energy. I can't help thinking that this is one case where a controlled series of observations would be of real value.

Evan V. Shute, frcs(c), frsm
London, Ontario

P.S. One of my friends has taken 8,000 I.U. of vitamin E daily for many years; my wife has taken 4,800 for years and I 1,600 for years. No undue fatigue! Thousands have taken 1,600 I.U. or more. No ill effects.

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Nayar MC: Indian J Physiol Pharmacol 8:49, 1964

Side Effects from Vitamin E

To the Editor: "Fatigue Caused by Vitamin E" was the title of a letter to the editor by Harold M. Cohen, MD (Calif Med 119:72, Jul 1973), in which he described extreme fatigue and weakness experienced by himself, his partner and many of his patients on a starting dose of 800 international units d, alpha-tocopherol daily, and that "response to withdrawal of vitamin E was dramatic." His patients were described as "some with arteriosclerotic heart disease, but mostly men in their mid-thirties or early forties who were in excellent health . . ."

These observations are contrary to our experience in the clinical evaluation of vitamin E in various dermatological conditions of obscure etiology over the past eight years, during which we have administered d, alpha-tocopheryl acetate in daily doses ranging from 400 to 1,600 international units to several hundred patients, including myself, my wife and two girls on our office staff. There has not been a single complaint of fatigue or weakness.

The only side effects we have noted have been beneficial ones. Early in our investigation, one patient, who was being treated for a dermatological condition, mentioned that since taking vitamin E he had ceased having nocturnal leg cramps. Since both my wife and I were having severe nocturnal leg cramps, and two members of our office staff had suffered from the restless legs syndrome, we all began taking vitamin E about three or four years ago and have continued ever since, on dosages ranging from 800 to 1,200 international units daily, with practically complete control of the muscle spasms, and no evidence whatever of fatigue or weakness. Other types of muscle spasms which have responded partially or completely to vitamin E include intermittent claudication, nocturnal rectal cramps (three cases), and exercise cramps. Our preliminary report on leg cramps[1] was confirmed by Cathcart in over 100 patients in a private orthopedic practice.[2] At least half a dozen patients who were being treated for dermatological conditions experienced another beneficial side effect in the form of relief from anginal pain, so that they were able to reduce or to discontinue nitroglycerine.

Several investigators have pointed out that patients with severe hypertension, badly damaged hearts or diabetics on insulin should be started on small doses of vitamin E (100 international units daily), which can be increased gradually; otherwise complications may ensue. Since inorganic iron inactivates vitamin E, it should not be taken at the same time.

We have published a number of papers on our personal experience with vitamin E, as listed below. Vitamin E is by no means a cure-all, but it has a wide range of usefulness because of two important functions. On the one hand, its antioxidant effect prevents or retards lipid peroxidation of unstable lipoprotein membranes of tissue cells and intracellular organelles, while at the same time, through interaction with enzymes and other substances it promotes oxygen utilization in the normal process of living.

Dermatological conditions, some hitherto virtually untreatable, which in our experience have responded to vitamin E in doses ranging from 800 to 1,600 international units daily, include epidermolysis bullosa, pseudoxanthoma elasticum, scleroderma, morphoea, lichen sclerosus et atrophicus, Raynaud's phenomenon with gangrene, granuloma annulare, necrobiosis lipoidica diabeticorum, porphyria cutanea tarda, yellow nails syndrome, discoid lupus erythematosus, subcorneal pustular dermatosis, and both Darier's disease and pityriasis rubra pilaris, when combined with vitamin A.

It should be noted that Dr. Cohen administered d, alpha-tocopherol, while we prescribed d, alphatocopheryl acetate, the latter being more stable, but I doubt if this difference could account for his observations of fatigue, which are completely at variance with our experience.

SAMUEL AYRES, JR., MD
Los Angeles

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Sickle Cell Trait in the Sky

TO THE EDITOR: In their article on counseling patients with sickle cell trait (Calif. Med. 119:1-7, July, 1973) the authors assert that persons with Hgb-AB stand in special risk of vaso-occlusive phenomena when exposed to "unusual hypoxic situations" such as flying at rest in unpressurized aircraft above 6,000 feet. It would be unfortunate if such an assertion were to result in confusion about the degree of risk involved, and thereby tend to inhibit persons with the sickle trait from making free use of air travel in modern commercial aircraft.

The authors cite a report by Green, Huntsman, and Serjeant in the British Medical Journal to support their advocacy of caution on the subject. It should be noted however, that the referenced report concerns patients with either sickle disease (SS) or mixed hemoglobinopathies (SC, or STh). These latter mixed states, unlike the simple trait, are known to produce mild clinical manifestations of sickle disease. Only one of the eight cases in Green's original article was felt to be a true sickle trait and the authors themselves later recognized this fact and withdrew the case from their series in a letter published subsequent to the article (Brit. Med. J 3:294, 1972).

Actually, there is no convincing evidence to prove that subjects with the simple trait suffer any special vaso-occlusive risk from exposure to a reduced pressure environment in the first place. Published reports which have claimed such a risk are invariably anecdotal and retrospective in character and most of them appeared prior to the availability of electrophoretic methods for differentiating the mixed hemoglobinopathies from the simple trait. Commercial aircraft in current use, although pressurized, still operate at cabin altitudes equivalent up to 7,500 feet, yet thousands of passengers with sickle trait routinely travel by air without jeopardy, and many airlines (including United) employ flight cabin attendants known to have the sickle trait.

C. F. CATLETT, MD
United Air Lines
Jamaica, N.Y.

The Authors Reply

TO THE EDITOR: The risk that an individual with sickle trait might develop an infarct at high altitude is certainly minimal, but it is important that this risk be recognized at least by medical personnel. Dr. Catlett is correct in noting that there is now no adequately documented case of a crisis in a patient with sickle trait alone, due to flying in a pressurized aircraft. However, splenic infarction in sickle trait individuals travelling at high altitude, but not in pressurized aircraft, has been established in more than 15 cases.[1-3] The exact risk for the sickle trait individual in commercial aircraft will only be determined with further experience. Factors other than exercise and hypoxia must be involved since no sickling crises were reported among the athletes with sickle trait that participated in the Olympic Games in Mexico City at an altitude of 7,000 feet.[4] Similarly, no problems related to sickle trait are reported among the 39 players in the National Football League who frequently travel by air and may play at altitudes of over 5,000 feet.[5]

We agree that the individual with sickle trait should not be discouraged from travel in pressurized aircraft.

W. BYRON SMITH, MD
W. C. MENTZER, MD
PETER R. DALLMAN, MD

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Congenital Syphilis in Newborn

TO THE EDITOR: When reading the article by Teberg and Hodgman (Teberg A, Hodgman J: Congenital syphilis in newborn. Calif Med 118: 5-10, Apr 1973), I could not help but wonder about the numerous residents, interns, pathologists, nurses, other hospital personnel, and relatives who were exposed to these infants, especially Cases No. 5 and 6 with their profuse nasal discharge of *Treponema pallidum*. What measures, if any, were taken to investigate the spread of the infection among these exposed individuals?

GLENN C. SZALAY, MD
Harbor City

The Author Replies

TO THE EDITOR: Dr. Szalay's concern for the need for protection of personnel exposed to infants with congenital syphilis is justifiable. At this time we do no routine serologic follow-up on house staff or hospital personnel. Dr. Willis Wingert, Director of Pediatric Out-Patient Department, emphasizes to the house staff during their orientation the potential hazards inherent in contact with infants with congenital syphilis. He carefully instructs house officers that any infant with purulent rhinitis and/or eroded diaper rash must be managed as potentially contagious.

Surveillance of infection spread in our hospital is through the Infection Committee. To date, no record of syphilis spread has been recorded. Although current hospital policy does not require formalized follow-up serologic examination of contacts, all personnel involved with the infant are appraised of the potential hazard and urged to secure serologic tests if indicated.

ANNABEL TEBERG, MD
Associate Clinical Professor of Pediatrics
Los Angeles County/USC Medical Center
Los Angeles

Refer to: Moore FD: Backlash: The case for American medicine.
Calif Med 119:76-83, Oct 1973

Backlash

The Case for American Medicine

FRANCIS D. MOORE, MD, *Boston*

THE GOLD HEADED CANE symbolizes a certain kind of physician: a prototypic educated gentleman such as Mead or Sydenham, concerned for his patients, above the cares of the market place, joining science and art at the bedside, concerned with base politics only to the extent that his consultation is sought by royalty (as Radcliffe's was by King William and Queen Mary) thus adding prestige not only to his name but to the profession as a whole.

Can this precarious reality or even this hallowed image be preserved in a day when all of medicine is swept up in politics?

By the way, what *is* (or are) politics? Politics has been defined as "the art of the possible" or the "poisoned perfidy of popular power," or the "process of upward mobility in a power structure." Actually the definition I like best is: "Politics is the process of bringing others to your point of view." It is a sort of seeking agreement by seeking affection, seeking votes by seeking backers, or making progress by making friends. Politics implies persuasion; it only has value in a society where the weight of persuaded opinion is operationally effective. Politics implies that persuasion is not done by force or violence; violence on the body of a person rarely changes his mind. If violence is used or the rights of others infringed, politics has degenerated into crime or war.

Doctors today are swept up in the political process because, increasingly, society feels a sense of ownership or proprietorship of doctors and of the whole medical profession. Society perceives that it has selected the medical students and paid for their education and will therefore govern their service. Society wants to decide who will get the Gold Headed Cane and what he will do with it.

Public proprietorship of medicine has been growing steadily in all the societies of Western Europe, Canada, Australia, New Zealand, and parts of South America since World War II when the National Health Service was established in Great Britain. There is no other profession that is so cherished by society that they want to hug it to death and control it completely. Architects, lawyers, and clergymen get off scot-free.

Proprietorship of medicine expresses itself by statutory legislation, payment mechanisms, and constraining regulations. Physicians must play a major role in the political decisions that lead to such laws. As physicians seek to bring others to their point of view, they are engaged in the political process.

Physicians in politics will always be accused of speaking only for themselves as providers when, in point of fact, there is no one else who can speak so eloquently for the consumer—the patient—based on centuries of collective experience. Most "consumers" who speak so loudly are actually quite healthy and know little of mass disease. Legislators would have us believe that they speak for the afflicted, but they never do. It is only the physician who sees and works daily with the lame, the old, the halt, the blind, the suffering, and the dying; it is a part of our professional com-

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William J. Kerr lecture presented at the Annual Gold Headed Cane ceremony, University of California, San Francisco, June 2, 1973.

The author is Moseley Professor of Surgery, Harvard Medical School, and Surgeon-in-Chief, Peter Bent Brigham Hospital, Boston, Massachusetts.

Reprint requests to F. D. Moore, MD, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston, MA 02115.

mitment to speak for them in the political arena.

Professional politicians speak to special problems that they see as important, such as cancer or heart disease; in many cases they speak with special emotion about some special medical problem that has recently afflicted their own family. Such categorical concern is a gross injustice to those thousands who suffer equally severely from other less prominent ailments. In no case has the politician in recent memory really spoken for the whole collectivity of ill patients. How can he? He's never seen them more than one at a time!

To participate in the political process is not an accustomed feature of the American medical tradition. In becoming embroiled in politics, physicians should be aware that career politicians seek simplistic explanations, and provide simplified solutions for complex problems. Such monolithic solutions are in fundamental conflict with any rational, intellectual or scientific understanding of our complex society.

As physicians we realize that appearances are often deceptive. The tall, thin, worrying man with abdominal pain may actually have gallstones while the little fat mother-of-six might have a duodenal ulcer. We realize that disease, human nature, and society have many complexities rarely to be categorized under a single heading or understood at a glance. We must never fall prey to simplified solutions for complex problems and we must engage in politics with the principal objective of keeping the politicians close to the reality of sickness and the real health care needs of our society.

It is my conviction that the younger generation of men and women have had a greater experience with politics than anyone of my older generation. You have generated effective political pressures for peace in Southeast Asia, for consumer representation in corporations, for student participation in university governance, for broadening of the educational establishment.

It is to none of these issues that I address myself here, because I feel you know more about them than I do. Instead I would like to consider the position of American medicine in relation to its over-simplified political image. This is kind of a realistic backlash; I believe there is a place today for medical students and physicians to join in the backlash. We must describe some of the complex configurations in American society that demand a more realistic approach than those that travel under the labels of "liberal" or "conservative." Simple polarization of political extremes will solve none of the problems of American medical care.

One of the difficulties of political polarization in dealing with complex social questions is the blind dislike—even hatred—that persons generate across the abyss. The liberal thinks of conservatism as nothing but organized selfishness, acquisitiveness, a desire to maintain personal position or wealth, and outright laziness. In return, the conservative sees the liberal as a ruthless radical, head-in-the-clouds with lofty ideals, totally impractical and ready to sacrifice the freedom of others to promote (but rarely achieve) a theoretical objective. These mutual images are destructive of any sort of creative or realistic problem-solving. It is notable that in the past 50 years nearly all occupants of the White House (as well as many senators and congressmen), once elected, and with the rhetoric behind, have abandoned their campaign polarization in order to get the job done in practical terms.

Detested, But Loved and Wooed all the Same

First off, let us consider one of the most remarkable features of American medicine today. Never has it been under such severe criticism, never have so many books been written about its faults, never have so many bills been introduced into the Congress to change it. But never has it been so attractive to the young.

The figures are spectacular. About five years ago there were 9,500 openings in the first-year medical class in the United States, and there were 18,000 applicants. Three years ago the figures climbed to 20,000 applicants for 11,500 openings. Two years ago this rose to 37,000 applicants for 13,500 openings and now in 1973 there were 70,000 applicants for 14,000 openings.

In addition, there is a flood of graduates from foreign schools entering the United States. The influx has risen from about 500 a year up to the end of World War II, then to about 700 annually toward the end of the 50's, and now this has risen to the spectacular total of 5,000 in the single year 1972.

Thus, by 1976 we will find approximately 22,000 people entering medical practice in the United States, as contrasted to the figure of about 10,000 a year only seven years before.

There are two points that need to be made about these remarkable numbers.

First, *beware of the popular political and sim-*

plistic notion that there is a great shortage of doctors in this country! It is highly doubtful that there ever was a shortage and there certainly will not be a shortage in the next 25 years. Actually the number of doctors in this country (165 per 100,000 population) is as high as it has ever been and will shortly rise by approximately 20 percent to 185 per 100,000 in about 1985. This increase in physicians entering practice is going to move us rapidly toward a surplus. There is no evidence that any of the ills of American medicine will be cured by providing doctors to the number of 185 to 200 physicians per 100,000 population. Our current ratio at 165 is more doctors per capita than are found in any other country in the world today. Adding 20 percent to this, without changing distribution or recruitment into primary care, will do nothing for American medicine.

There is nothing more useless to patients than underoccupied specialists. And while it sounds snobbish to say so, it is a real hazard to the intellectual, ethical, and scientific standards of American medicine, when almost one-third of the annual input are physicians educated in other countries, many of them lacking English as their native tongue, lacking the parliamentary tradition of the English Common Law, and from overcrowded medical schools where the emphasis on biological science and ethical humanism is minimal. Several schools in Southern Europe and Asia have as their main attraction the export of doctors to the United States.

The second challenge provided by these figures is for us to identify those components of American medicine that make it so attractive to the young. Some might say that the attraction was money, a high income, social position, or postponement of decision. My own conviction is quite different. Biology is the most fascinating of the sciences and humanism is the most attractive of the arts. Putting them together makes a uniquely attractive career. In addition, American medicine is still blessed by that most overworked and under-realized of political attributes: freedom.

The freedom of American medicine is not merely to do what you wish, or to injure people, or to have two days off a week, or to make thousands of dollars. It is a freedom of career pattern and career choice, freedom of maneuver over the years. This aspect of American medicine is still very prominent and makes American medicine spectacularly attractive.

In any system of national regulation or legislation some of these career freedoms will be lost. Most of us will be quite content to lose some of these freedoms if we can improve medical care by that loss. If by losing some of our own freedom, more patients truly have freedom of access to care and freedom to achieve greater security in their health, we will welcome the change. But we should understand what an attractive thing this freedom of the American medical career is, and we should not lose it or sacrifice it carelessly or thoughtlessly.

Legislators are notably willing to spend someone else's money! It is important to realize that they are also quite willing to do away with the freedom of others, particularly the freedom of health professionals.

American Medicine: System or Non-System?

Another conventional accusation is that American medicine is a "non-system." People who say this simply do not understand all the interlocking systems within American medicine which range from medical school admission to internship appointment, to the American Board examinations, to modes of practice, channels of patient referral, hospital regulations and the rest. Many of these systems lack perfection; their greatest strength is that they co-exist in a pluralistic society. Their greatest weakness is that they are complex and demand some understanding; the system of patient entry, triage and referral often denies care to the uneducated and the underprivileged.

Those who accuse American medicine of being a non-system imply that we would be better off if American medicine were a single, National System. We are therefore entitled to ask, "What kind of a system do we have in this country that provides a national systems-model for medicine?"

Well, we could start with some of the largest systems in the country, the military—the Army, Navy, and Air Force. Somehow the Pentagon is not just exactly the model that we seek in medicine. It is top-heavy, wasteful, anonymous, impersonal, and almost impossible to deal with.

The national railroad system is not a very good model. When it became unprofitable, it produced its own selective dissolution by making itself totally unattractive to the consumer.

Another big system we could look at is the government itself. Surely that is the largest system we have. Although it has many great strengths, it is capable of severe disarray from top to bottom.

In this country of 200 million people it is not easy to point to a National System that is unified, clean, free of corruption and a satisfactory model after which a new medical system might be patterned. Maybe we are better off to keep the systems we have—small, capable of interaction, pluralistic. At the same time we should open up the system of entry, payment, and care more satisfactorily for those who do not readily adapt to such a multiple choice arrangement.

Should an Industry Be Cottage or Non-Cottage?

Another criticism that deserves a heavy backlash is the statement that American medicine is still a "cottage industry" consisting of one doctor talking to one patient in his little office over the corner drugstore. This concept, that American medicine is faulted as a "cottage industry," became rooted in the sociologic literature about a decade ago. The time has come to root it out.

There are communities in this country, some of them large cities, where the medical industry is one of the largest employers. Rochester, Minnesota, and Galveston, Texas, are two examples. In several instances, municipal hospitals are the largest single line-items in the city budgets. Boston is an example. Due to the rising cost of hospital labor, most hospitals have seen their budgets quadruple in the last 20 years. My own hospital in Boston has seen its annual budget increase from $5,000,000 to $35,000,000 in the course of the last 25 years with only a 30 percent increase in size. And these labor costs are not for the pay of doctors or nurses. They are mostly the labor costs of the semi-skilled hospital employees that make up the majority of the workforce. When somebody states that medicine is a cottage industry, my retort is, "Some cottage!"

But, again, like the "non-system" criticism, this implies that if American medicine is a cottage industry, then there must be some other kind of industry, presumably non-cottage in nature, that one should emulate in restructuring American medicine.

Would this be General Motors, for example? Without meaning to give offense to any Chevy owners or GM stockholders, I will state that after 45 years of driving American cars I have seen these products get larger and larger, deteriorate in quality and durability. All of them look alike, they are advertised to drive easily at speeds that are illegal and unsafe, and they are extremely wasteful of gasoline. One small lady weighing 100 pounds driving around New York City in a Cadillac weighing three tons represents the most shocking waste of fossil fuels imaginable; she is a one-woman energy crisis. It is very difficult to conceive that this non-cottage industry has produced anything very noteworthy, save for its annual dividend record.

The television industry might be another example of a non-cottage industry. Crass commercialism, catering to the lowest taste of a dimly perceived "general public," unable to accommodate educational material without special subsidy, the American television industry would hardly seem to be a model for American medicine.

In point of fact it is the small or strictly cottage aspect of medicine—one doctor talking with one patient—that is the most important single aspect of medicine that we must at all costs try to maintain in any new system. The National Health System in Great Britain, surely the most successful of the nationalized services in Western Europe, is now undergoing an agonizing reappraisal. This new national inquiry is more searching than any the National Health System has undergone since its inception 25 years ago. The prime target is improvement in the relation of the doctor to his patient and particularly of the general practitioner to his public. The fact that it is becoming increasingly difficult in Great Britain for patients and doctors satisfactorily to achieve this simple one-to-one relationship, symbolized by the Gold Headed Cane, stresses the problems inherent in any national organization of medical care.

The fundamental act of medical care is the assumption of responsibility for the welfare of the patient. This is an event that occurs at a single moment in time between two people, often by a glance, or by an unspoken contract achieved by an affectionate pressure of the hand or by mutual assent to forward planning. There is no substitute for this act of personal responsibility. It is this which the sick patient seeks, more than any other quality in medical care: "I will put myself in your hands."

Some of the worst aspects of American medicine arise from difficulties patients have in achieving this relationship, and that doctors experience in finding an ambience that is small and simple enough to make the relationship meaningful, and to which large numbers of people, from the underprivileged to the sophisticate, will have access. Surrounding a physician with elaborate "non-cottage" equipment, diagnostic aids, automated laboratories, allied health personnel and computers, will achieve absolutely nothing in the absence of this mutual and personal trust between two people.

From our visits to other countries this past year, including England, Sweden and Norway, we can say that drastic changes in health care that create large unified national health services and obliterate anything that might be called solo private practice do indeed give medicine a look that is "non-cottage" in character. They have not been universally successful in meeting this basic objective of medicine: a personal contact between two people that is based on shared respect and responsibility.

Which Should We Be, Generalist or Specialist?

Another problem perceived by many of the public, students and congressmen is the classic enigma of the generalist versus the specialist. This is a fine example wherein doctors in politics must avoid simple generalizations, and see reality in the full round. We can all agree that in this country today there are not enough people readily available for the primary or generalist family-doctor function. And yet that function is quite meaningless unless the specialist is also there to provide highly skilled back-up to the family physician.

Everyone is against specialization except the patient. That same writer who denounces specialization as a major vice of American medicine will change his tune when his wife turns up with a brain tumor or a solitary obstructed kidney. He will then set about trying to find the man or the hospital unit that has had the greatest experience with that particular problem. He will not only seek the specialist whose existence he deplores, but even a superspecialist.

It is therefore our job as physicians in the political process to remind the public, the politicians and even our medical school deans and curriculum committees, that American medicine must always have an effective balance between the primary care physician and the specialist. We acknowledge that the poor farmer in the backwoods of Mississippi or Alabama who cannot empty his bladder, or the distraught grandmother in the black ghetto who cannot see, have severe troubles finding a family practitioner; we also must acknowledge they also have extreme difficulty in making arrangements to have the enlarged prostate or the opaque cataract removed.

Consumerism Versus Elitism

Closely related to this problem of specialization is the political and social issue of consumerism versus elitism in hospital staffing. Again we are dealing with ambivalence. We must learn to live with it, describe it, defend it, and strengthen it, rather than pulling ourselves apart by adopting one extreme view or another.

Some persons feel that hospital staffs should be wide open so that any physician with a license to practice can join the hospital staff, admit patients, and do whatever he wants to treat them. Surely this would seem to be the simple democratic way in a populist-dominated liberal society.

On the other hand, there are those who feel that physicians on hospital staffs are responsible for maintaining their special skills, that they should demonstrate continuing education and maintain credentials for whatever they are permitted to do; that they should be re-certified from time to time and demonstrate a track record of responsibility and effectiveness in their chosen work of special skills.

These two points of view often come into conflict that would be amusing if it were not so serious a matter. For example, there are two lawsuits now pending that epitomize this issue. In one, a patient was treated by a physician inexperienced in the appropriate specialty, who was on emergency ward night coverage. The case-outcome was very poor, and the patient filed a lawsuit. The significant point was that the patient did not sue the physician. Instead, he sued the trustees of the hospital! He contends that it was the job of the trustees to see to it that no one without appropriate special qualifications should be permitted to render a professional service that requires special skills and is potentially hazardous to the patient. We can all agree that this patient was quite perceptive: hospital trustees do have some responsibility in this area!

On the other end of the scale is a lawsuit now pending and being brought against some hospital trustees by a young practitioner. He is a well-educated young physician who is interested in family practice. He wished to maintain his independence and therefore did not opt to join a large group practice that had come to dominate the community hospital. He was told that he could not become a member of the staff of that hospital because he did not have suitable credentials for any of the specialties that the group practice required. And yet, he wished to live in that community and give a service to the people there. He is suing the hospital for permission to achieve staff membership, and I believe that many can see his point!

Maybe the title of this lecture should have been "Ambivalence." As scientists we learn to see both sides of problems, and as physician-politicians we must persuade others to see likewise.

Fee for What? Service, of Course

The term "fee for service" has at least two meanings.

For the patient, it connotes that his pain in the belly might cost him $15 or $15,000, according to whether it is green apple colic or cancer of the pancreas. This type of bioeconomic alternative is simply unjustified for the unsuspecting patient, who has no way of controlling what caused all that pain in the first place. This aspect of fee for service is obliterated by any sort of insurance plan or prepaid mechanism.

The other meaning of "fee for service" suggests that the doctor is paid on a unit basis for the service he performs. From an ethical point of view, we might readily agree that this is quite a good thing if it prevents doctors from being paid for doing nothing! On the other hand, it can make medicine into a happy hunting ground and a medical registration into a hunting license, with the achievement of very large income for a very few people. Much of medicine and all of surgery has an interesting "centripetal" aspect: success breeds success. Referral is always central on the spinning wheel, never peripheral.

In its simplest form, fee for service gives the physician a simple incentive to do that extra work which is so much a part of medicine and to put in extra effort into what may, at times, be a boring and repetitive task. Buried somewhere in this tradition is the fact that special devotion to the needs of patients and a meritorious record of service are to be rewarded. Incentives can be provided by other means: promotion, awards, special clinical privileges, or unit leadership. It certainly can play an important role in medicine. Its notable absence in Sweden, for example, is regarded as a major cause of loss in quality of care.

The recognition of this beneficial aspect of fee for service has led to a change in its name to "incentive reimbursement." In the special language of the legislator and the sociologist, this seems to be more acceptable.

Fee for service also introduces a restraint on those persons who would employ the doctor merely as a sounding-board for petty neurotic complaints, or on those ignorant and thoughtless persons who, having experienced a headache and diarrhea for 48 hours, elect to call the doctor at midnight. This sort of thoughtless use of the medical profession is much less prominent when fee for service plays a role.

Some physicians need an incentive, some patients need a dis-incentive. Can some element of fee for service be retained for both?

Government or Governance?

Finally, we come to the clincher: "Should some aspect or arm of the United States government take over American medicine?"

One of our congressmen who has introduced legislation along this line pursues his case by an essentially episodic approach. Both in his public hearings and in his book, as well as in his speeches and platform appearances, he selects a series of isolated examples wherein some aspect of medical care in the United States has been faulty. He moves from the sad anecdotes to the concept that national legislation is essential.

I have often imagined the privilege that I might sometime have, of sharing the platform with him, and treating of my contacts with the federal government in a similar episodic way. I can tell some truly remarkable stories of capricious changes in budget, reversal of decisions, coming and going of key officers without telling the troops, changes in government policy with changes in White House administration, corruption and maladministration, blacklisting of scientists for political purposes, and the misuse of the fund-granting power of the government to accomplish political side-issues. An amusing example of the latter is the withholding of funds for research because an institution did not employ enough Spanish-speaking doctors! How ridiculous can we get?

I would like to ask, on the basis of these ridiculous episodes of governmental vagaries, do we really want American medicine to be conducted in such a way?

There has been a recent proposal that the government pay all the interns and residents in the country, to save money for the patient. Actually, the cost of residency training is but a minor feature of the cost of national health care. Even in teaching hospitals with large resident staffs, it only amounts to about 8 percent of the day cost. Were such legislation to be passed, every congressman would want his own local hospital (for which he feels strong affection and loyalty because of the way they took care of his family) to acquire its full share of residents, quite regardless of its educational potential.

A much better project for the federal government in 1973, 1974 and 1975 would be to put its own house in order with a system of health care that the federal government now owns and operates *in toto* with many hospitals, doctors and a huge administrative staff.

Federal Medicine . . . Right Now!

In considering American medicine, it is easy for us to forget that the federal government now operates a large system of medical care with federal ownership of all the hospitals and payment from taxation for all the doctors' salaries, with a patient population that at its peak totalled upward of 25,000,000 people, and now has about 17,000,000 potential patients. This system, the Veterans Administration, works remarkably well for just one sort of care—in-hospital, specialty consultative medicine for just one sex (96 percent male) and one age group (adults—largely over 25 years of age). Here is a federal system of medicine, completely supported by the taxpayers of this country, that does not provide family care, primary care, preventive medicine or house calls. We are so accustomed to this federal system of Veterans Administration medicine, initially established in gratitude to those men who served in the last two wars, that we do not recognize its truly ridiculous absurdities. Where is the legislation to fix it?

For example, a man who built Liberator bombers on the assembly line at Willow Run now has a broken back. He will soon have a broken bank, and a disabled family as a result. But if his draft number had come up a little differently and he had flown the bomber over Europe, his broken back would be taken care of free of charge for the rest of his life. We will all agree that there is no longer any justification for making such superficial social distinctions for the privilege of federal tax-paid medicine, according to how your draft number happened to hit the capsule in 1942.

And yet, for all the generosity of Veterans Administration medicine, the very same man who flew that bomber and receives all that free care finds many inadequacies in the system. Were he to call that same hospital at night, and tell the admitting officer that his wife was bleeding, or that his child had a temperature of 106° and was having convulsions, he would simply get no useful response. How could we spend so much money, build so many buildings, and have such a huge superstructure of administrators in Washington, out of gratitude to our veterans, and then let the systems degenerate and disintegrate into such an inflexible and totally inappropriate system of medical care 25 years later?

At a recent meeting of the Deans' Committee at the Veterans Administration Hospital near us, we were discussing the expansion of the hospital benefits so as to include the community, not only because the hospital was half empty, but because it provides services that are very hard to get anywhere else. The director of the hospital stated that if anything like that should come up in the papers, he would be deluged by telephone calls from veterans' organizations claiming they were losing their rights.

For any veteran of the wars of this century who claims that he owns or has special rights in a VA hospital, we should remind him that these are being paid for by all of us, and that the bill is very large. The VA hospital system is owned by the taxpayers of the United States. The voters of this country should press hard to open the system up so as to provide special services that are needed by each community. We should insist that this system of federal medicine serve the whole people without respect to the patient's previous state of government servitude.

Something for Everybody

Well, this talk of mine might be thought of as having something for everyone. Whether you wear the long beard of chronic discontent or the well-clipped preppie hair-do of conservatism, there seems to be something here for you. But that's the way it is: Simple political polarization does not fit any realistic view of medicine.

Many of my fellow surgeons think of me as being a bit in the left-wing in my thinking. A Harvard Professor—after all, what else can you expect? I am grateful to them for their toleration.

But most sociologists with whom I work think that I am an incorrigible conservative, the very prototypic short-haired, surgical right-winger.

I am very proud of this total confusion as to my political posture because none of the problems of American medicine is amenable to solution by adopting a posture at one end of a conventional political spectrum and waving a flag that is labelled "radical" or "conservative."

I commenced this lecture by intimating that all doctors are going to be swept up by politics, and it may be that in another five years it may be hard to tell the Gold Headed Cane from the Gold Headed Gavel. Maybe the moral of my talk is that the Gold Headed Gavel should always be in the hands of a physician well qualified to carry the Gold Headed Cane. He must have the same sort of personal experience in the care of the sick, the same hesitation before adopting a simple diagnosis or a single cure and the same humanistic desire to get along with people so that when he joins the political process he can teach others to stop, look, listen, and think before they operate. Such a physician will always be accused of fuzzy thinking and ambivalence. But in the end he will be right.

The three greatest faults of sociologic and economic thinking relative to medicine are premature crystalization of a point of view, factual error due to remoteness, and obsolesence of the data base. Reality is like shifting sands under the keel of the anchored scholar.

One of the difficulties of fashionable ideas is that they go out of fashion. In the last ten years it has been very fashionable to criticize all aspects of American medicine. The crystalized and fashionable ideas of American medicine need a backlash. It has been provided in part by Mr. Schwartz's book, "The Case for American Medicine," from which the title of my talk is borrowed.

In keeping with all of this, as a physician-politician-citizen, I should go out on my political limb and identify the points that I think are most important for us to push for in these next few political years. These are the "Lucky Seven" points of my own platform:

1. *Beware simplistic solutions* and do not let yourself get backed into a conventional political posture. Maintain the freedom of option that is characteristic of career patterns in American medicine, and of the practice of medicine itself.

2. *Beware of the doctrine of a doctor shortage* in these coming years. Any evidence that there was a shortage even in the recent past was very slim, and is now rapidly disappearing as the yearly input of physicians is becoming a flood, doubling in ten years. There could be nothing worse for American medicine than a huge oversupply of physicians, many of them from other countries. This will lead to an overgrown and underfed profession, searching for ways to bolster its income.

3. *Tighten up hospital credentialing.* Require evidence of continuing education for everyone on the hospital staff who undertakes hazardous services to the sick, be he surgeon, general physician, psychiatrist, pediatrician, or radiotherapist. Place a ceiling on malpractice claims so that the cost of medical care will not be further increased by the cupidity of lawyers.

4. *Encourage primary care as a dignified, professional field,* involving special skills, akin to the other so-called specialties. Decrease the production-rate of the defined specialties by choking off those residency programs that are unsatisfactory and unsuccessful in producing candidates who can pass the examinations. Give this job of weeding-out to the American Boards and their co-ordinating councils.

5. *Improve the distribution of physicians* by making known to interns and residents the location of those communities where their presence as practitioners is most needed.

6. *Require by law that every family in the country have catastrophic health insurance.* Provide cost-underwriting for the poor by the use of tax funds by state, local, and federal sources. Take this step without yielding to the political temptation to take over the entire practice of medicine by those political entities that constitute the payment source.

7. And last, recognizing the absolutely prohibitive cost of building new hospitals today, *revise the Veterans' Hospital system* from top to toe so that these many huge hospitals, with their expensive supply logistics, paid for by the taxpayers of this country, can provide adequate medical care without regard to race, creed, color, sex, or previous condition of government servitude. Devise new service concepts for these hospitals that will be adapted to the local needs of each community and give services not otherwise available. Then, instead of becoming aging, expensive and half-empty monuments to a grateful nation in 1946, they will become an essential feature of American medicine.

Well, this talk was supposed to be inspirational and not conspiratorial! Above all, I want to thank you for the honor of being asked to give the William Kerr Gold Headed Cane Lecture, and to become a part of this ceremony which contains so many of the elements that we all wish to retain in American medicine both now and in the future.

Information

CLINICAL CARDIOLOGY SERIES

Systolic Time Intervals

A Non-Invasive Method to Determine Left Ventricular Function

RALPH SHABETAI, MD

Material Supplied by the American Heart Association

MEASUREMENT OF SYSTOLIC TIME intervals was developed as a technique to allow the clinician to assess the function of the left ventricle in a non-invasive manner. These intervals are obtained with the following simple instruments:

A microphone placed on the precordium to register the first and second heart sounds distinctly.

A transducer placed over the carotid artery to record its pulse contour with sharp onset and precise dicrotic notch.

Conventional electrocardiogram electrodes to define the exact time of the onset of the QRS complex.

The three signals obtained with these devices are recorded on a three-channel strip chart recorder at a fast paper speed, preferably 100 mm per second.

The left ventricle does not squeeze blood into the aorta slowly, as one squeezes juice from a lemon, but abruptly forces blood through its orifices. During isovolumic systole, a 50 millisecond period when the aortic and mitral values are both closed, the ventricle develops tension. Near the time of peak tension, the aortic valve opens and the left ventricle rapidly ejects two-thirds of its content into the arterial system before the aortic valve again closes. Hemodynamic studies show that a normal ventricle, or a ventricle being stimulated pharmacologically, develops isovolumic tension more rapidly than a diseased ventricle, or one exposed to agents with negative inotropic effects. In addition, it has been demonstrated that left ventricular ejection time (LVET) varies directly with stroke volume. Thus, short isovolumic systole, large stroke volume, and long ejection time characterize normal left ventricular function.

LVET can be approximated easily by recording the time between the onset of ejection and dicrotic notch of the externally recorded carotid pulse. Weissler and associates calculated pre-ejection period by subtraction. They measured "total electromechanical systole" as the interval between the onset of the QRS complex and the first major component of the aortic valve closure sound. From total electromechanical systole they subtracted the left ventricular ejection time determined from the external carotid pulse tracing. The difference yielded the pre-ejection period of systole (PEP). PEP includes the electromechanical coupling interval as well as isovolumic systole. However, hemodynamic studies have shown that PEP varies proportionately with isovolumic systole. Thus, Weissler's work divided systole into externally measured pre-ejection and ejection periods, and showed that normal ventricular function is characterized by a short pre-ejection period and a long ejection period. Not surprisingly, the ratio PEP:LVET is a more sensitive index of ventricular function than the numerator alone and, certainly, than the denominator alone.

Clearly, mechanical events in the heart and arteries are time dependent. Thus, the PEP associated with a fast heart rate is less than that seen with a slow rate, and LVET with a fast rate is less than with a slower rate, because tachycardia occurs largely, although not exclusively, at the expense of diastole. Weissler and his associates, using data from thousands of patients, have developed regression equations from which normal PEP and LVET can be predicted as a function of heart rate. Other regression equations obtained show that PEP:LVET can be used to predict the ejection fraction, a sensitive ventriculographic index of left ventricular function.

Valvular disease alters the conditions affecting filling and emptying of the ventricles. Thus, systolic time intervals from patients with valvular disease are difficult to interpret. The technique has thus found its greatest application in detection and assessment of ischemic heart disease and myocardial disease. Systolic time intervals have also been

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employed to assess the effects of interventions, such as exercise, pacing, and drugs.

Measurement of systolic time intervals offered promise of becoming useful for serial study of left ventricular function, in patients in the coronary care unit after myocardial infarction, and in postoperative patients after coronary artery surgery. However, in both these areas, results have been conflicting.

How readily can these data be obtained? Reliable systolic time intervals can be recorded by any physician who has ready access to a high-quality multi-channel phonocardiograph, performs the technique frequently, is careful to assure high quality electrocardiogram, phonocardiogram and pulse tracings, has the time and patience to make accurate measurements, and understands the limitations of the method.

Can systolic time interval measurement ever substitute for cardiac catheterization to yield information that is not apparent from the history, physical examination, ECG and chest x-ray films? For a decade or more, the systolic time interval technique gained little acceptance and was not utilized by most cardiologists. As the need to evaluate left ventricular function increased, systolic time intervals became more popular. Unfortunately, the technique was frequently employed in a manner which its originators would deplore.

Measurement of systolic time intervals seldom yields data that surprise the experienced cardiologist. When considered in context, such measurements may supply useful information. Moreover, they have two cardinal virtues:

1. They can be performed repeatedly with no danger, little or no discomfort, and little expense to the patient; and

2. The results are quantitative. Thus, serial changes can be detected readily. Accordingly, measurement of systolic time intervals is likely to play an increasingly role in clinical cardiology and deserves continued energetic research effort.

Selected Items from the FDA Drug Bulletin

Intrauterine Devices

Precautions During Use

The Food and Drug Administration wishes to inform physicians that intrauterine devices (IUDs), being used by more than three million women in the United States for birth control, have not been subjected to premarket review by the FDA. Because of growing concern about the safety of some of these products, information from FDA files is presented here for physicians.

The mechanism of action of IUDs is not precisely known, but it is generally recognized to be dependent upon the foreign body reaction produced by them.

Sterile technique should be used in inserting an IUD. It should not be introduced in women who are pregnant, have a history of infected abortion or postpartum endometritis within the previous six weeks, have acute or subacute pelvic inflammatory disease, acute cervicitis, distortion of the uterine cavity due to myomas, or a recent history of abnormal uterine bleeding, or who have suspected uterine malignancy. Incidence of perforation on insertion is higher when insertion is performed early postpartum.

An estimated 10 percent of IUDs are expelled during the first year after insertion. Expulsion is more frequent among younger women and usually occurs during menses.

The pregnancy rate for each type of IUD has not been precisely determined. However, for the most successful types the rate is 1.5 to 3 pregnancies per 100 woman-years during the first year and lower thereafter. These devices are less effective than conventional oral contraceptives (0.3 to 0.5 pregnancies per 100 woman-years), but they are generally considered to be more effective than other mechanical methods of contraception.

There is no evidence that ectopic pregnancies are caused by IUDs. However, since IUDs markedly reduce the incidence of intrauterine but not ectopic pregnancies, the ratio of intrauterine to ectopic pregnancies is altered. No relationship between IUDs and premature or malformed offspring has been established although such incidents have been reported.

Major adverse reactions include excessive bleeding, pelvic inflammatory disease, imbedment, and perforation of the uterus. Abdominal perforation by a closed IUD may result in herniation of tissue through the closed loop. Therefore, a closed IUD should be promptly removed surgically when the diagnosis of perforation is made. Removal of an open device is optional depending upon the clinical situation.

Among less serious adverse reactions associated with IUDs are irregular bleeding, uterine cramps, pelvic pain, and backache.

FDA has received numerous reports of serious reactions associated with an IUD known as the Majzlin Spring. The danger of the device imbedding in the walls of the uterus increases the longer it is left in place. FDA is taking this opportunity to notify physicians directly about this hazard and is urging women using the Majzlin Spring to contact their physicians so that it may be removed as soon as practicable.

FDA's Obstetrics and Gynecology Advisory Committee prepared a detailed report in 1968 on experience with the marketed IUDs and FDA is undertaking another intensive review of all IUDs currently on the market. Proposed legislation has been introduced into Congress which would authorize FDA to establish appropriate controls for these devices. FDA believes at the present time that the IUD is an acceptable method of contraception which can be employed safely and effectively providing adequate precautionary measures are observed.

FDA Drug Bulletin, August 1973

Poison Prevention Packaging for Drugs

Under a law enacted in 1970, hazardous substances that may cause serious illness or injury in young children must be dispensed in child-resistant containers. In addition to safety caps the approved packaging may include any container which is sufficiently difficult for children to open. For example, unit packaging which requires the child to repeat the opening operation for each dosage unit may qualify.

Aspirin, except as an ingredient of powders and certain effervescent preparations, was the first drug to be so regulated. Next are all oral prescription drugs as of April 1974. An exception to this regulation is nitroglycerin, which must be readily available for emergency use by the elderly and must be dispensed in its original, sealed packet. Other exemption possibilities are under consideration.

The physician or consumer may request conventional packaging for any of the regulated drugs.

Additional over-the-counter drugs which pose accidental poisoning hazards to children under the age of five years are under consideration for safety packaging requirements.

FDA Drug Bulletin, August 1973

AMA Placement Service

The AMA's Physicians' Placement Service, which last year helped place an estimated 200 physicians, will exhibit at the AMA Clinical Convention in Anaheim. The meeting will run from December 1 through 5. The Service's 2,500 active physician resumés and listings of an equal number of openings will be available for the use of convention attendees at the Anaheim Convention Center. Included on Placement Service files are all specialties and most subspecialties covering all areas of the United States and some foreign locations.

The AMA Placement Service is free of charge to all registrants. Close association with placement services operated by state medical associations provides for wide circulation of physicians' resumés.

For additional information write the Physicians' Placement Service, American Medical Association, 535 North Dearborn Street, Chicago, Illinois, 60610.

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More to come in the November issue of CALIFORNIA MEDICINE

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

Atkinson, Ray Cook, Oakland. Died August 14, 1973 in Oakland of arteriosclerotic heart disease, aged 69. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1931. Licensed in California in 1931. Doctor Atkinson was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

Baer, Charlotte C., San Francisco. Died August 15, 1973 in Marin county, aged 65. Graduate of the University of California Medical School, Berkeley-San Francisco, 1941. Licensed in California in 1943. Doctor Baer was a member of the San Francisco Medical Society.

⁂

Barron, Henry Clinton, Jr., Riverside. Died August 7, 1973 in Riverside of brain tumor, aged 72. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1923. Licensed in California in 1923. Doctor Barron was a member of the Riverside County Medical Association.

⁂

Brotman, David M., Culver City. Died August 8, 1973 in Culver City of heart disease, aged 66. Graduate of the University of Illinois College of Medicine, Chicago, 1936. Licensed in California in 1945. Doctor Brotman was a member of the Los Angeles County Medical Association.

⁂

Conroy, Bernard J., San Anselmo. Died August 2, 1973 in Fairfax of heart disease, aged 71. Graduate of Washington University School of Medicine, St. Louis, 1931. Licensed in California in 1932. Doctor Conroy was a member of the Marin Medical Society.

⁂

Cutter, Robert Kennedy, Berkeley. Died August 9, 1973 in Berkeley of respiratory tract infection, aged 75. Graduate of Yale University School of Medicine, New Haven, 1923. Licensed in California in 1923. Doctor Cutter was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Eusden, Ralph B., Long Beach. Died August 5, 1973 in Long Beach of uremia and arteriosclerosis, aged 86. Graduate of the University of Nebraska College of Medicine, Omaha, 1918. Licensed in California in 1923. Doctor Eusden was a member of the Los Angeles County Medical Association.

⁂

Green, Berryman, Jr., South Laguna. Died July 4, 1973, aged 80. Graduate of the University of Virginia School of Medicine, Charlottesville, 1917. Licensed in California in 1930. Doctor Green was a member of the Orange County Medical Association.

⁂

Hanavan, Lewis Miller, Santa Clara. Died the second week of August, 1973 near town of Mendocino, aged 51. Graduate of Chicago College of Osteopathy, 1948, Licensed in California, 1948. M.D. degree from California College of Medicine, 1962. Doctor Hanavan was a member of the Alameda-Contra Costa Medical Association.

⁂

Hansen, Adolph M., Los Angeles. Died May 10, 1973 in Torrance of heart disease, aged 76. Graduate of Rush Medical College, Chicago, 1924. Licensed in California in 1924. Doctor Hansen was a member of the Los Angeles County Medical Association.

⁂

Harkins, James Edwin, Oakland. Died July 30, 1973 in Walnut Creek of heart disease, aged 56. Graduate of the University of Cincinnati College of Medicine, 1941. Licensed in California in 1946. Doctor Harkins was a member of the Alameda-Contra Costa Medical Association.

⁂

Lesko, Leo, Los Angeles. Died August 11, 1973 in San Fernando Valley of gunshot wounds in the chest, aged 44. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1958. Licensed in California in 1959. M.D. degree from California College of Medicine, 1962. Doctor Lesko was a member of the Los Angeles County Medical Association.

⁂

McMillen, Charles Howard, Jr., Los Angeles. Died July 14, 1973 in Van Nuys, aged 65. Graduate of the University of Colorado School of Medicine, Denver, 1933. Licensed in California in 1936. Doctor McMillen was a member of the Los Angeles County Medical Association.

⁂

Pope, Saxton Temple II, Orinda. Died August 27, 1973 in Berkeley, aged 71. Graduate of the University of

California Medical School, Berkeley-San Francisco, 1929. Licensed in California in 1929. Doctor Pope was a member of the Alameda-Contra Costa Medical Association.

⁂

RIGLER, STANLEY PAUL, Redondo Beach. Died August 8, 1973 in Palos Verdes Peninsula of myocardial infarct, aged 46. Graduate of Harvard Medical School, Boston, 1952. Licensed in California in 1959. Doctor Rigler was a member of the Los Angeles County Medical Association.

⁂

ROCHLIN, DONALD BRADLEY, Los Angeles. Died August 7, 1973 in Los Angeles of leukemia, aged 46. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1953. Licensed in California in 1957. Doctor Rochlin was a member of the Los Angeles County Medical Association.

⁂

RYPINS, RUSSELL F., San Francisco. Died August 18, 1973 in San Francisco, aged 79. Graduate of Harvard Medical School, Boston, 1920. Licensed in California in 1922. Doctor Rypins was an associate member of the San Francisco Medical Society.

⁂

SCHROEDER, RALPH L., Paradise. Died August 2, 1973 near Westport, Washington of heart disease, aged 69. Graduate of the University of Nebraska College of Medicine, Omaha, 1929. Licensed in California in 1937. Doctor Schroeder was a retired member of the Butte-Glenn Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

STEVENS, GEORGE ARNOLD, Beverly Hills. Died August 10, 1973 of heart disease, aged 68. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1930. Licensed in California in 1937. Doctor Stevens was a member of the Los Angeles County Medical Association.

⁂

WELLAND, FREDERICK HURD, Palo Alto. Died July 29, 1973 in Belmont, aged 39. Graduate of Harvard Medical School, Boston, 1959. Licensed in California in 1963. Doctor Welland was a member of the Santa Clara County Medical Society.

BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

DISORDERS OF THE RESPIRATORY TRACT IN CHILDREN—Volume I—Pulmonary Disorders—Second Edition—Edited by Edwin L. Kendig, Jr., MD, Professor of Pediatrics, Medical College of Virginia, Health Sciences Division, Virginia Commonwealth University, Richmond. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1972. 852 pages, $32.50.

The first few chapters, on pulmonary physiology and on therapeutic and diagnostic procedures, contain a wealth of useful data.

On the other hand, some of the chapters are more general, less focused and thus less usable. I found Mildred Stahlman's discourse on Respiratory Diseases of the Newborn to be in this category. For instance, while reference is made to the use of continuous airway pressure as a method of therapy, the details of how to apply this technique and in what settings are lacking.

On the whole this text is a very valuable one for anyone who finds respiratory diseases to be a major portion of his practice. It would also be of great value as a reference text for the library of any hospital or ambulatory facility caring for children. It may be a bit more detailed, however, than the average physician, resident or student would find to be necessary for his own individual use.

The second edition of this text follows the first one by five years. It appears in two volumes. This first volume covers diseases of the lower respiratory tract. A second volume, *Pediatric Otolaryngology,* takes up problems of the upper respiratory tract. This volume brings the material included in the first edition up to date and includes several new chapters, the best of which is on intensive care of respiratory disorders. The book includes a wealth of information on diseases of the chest in children. Most of the chapters are up to date and include much specific practical information. The best chapters are those on Asthma written by Susan Deer, on Cystic Fibrosis by Harry Schwachman and on Tuberculosis written by the Editor, Edwin Kendig.

MOSES GROSSMAN, MD

* * *

THE CHINESE ART OF HEALING—Stephan Palos. Bantam Books, 666 Fifth Avenue, New York City (10019), 1972. 256 pages, $1.50 (Paperback).

In his book, *The Chinese Art of Healing,* Stephen Palos, a Hungarian Buddhist monk, attempts to cover the principles involved and the treatment employed in traditional Chinese medicine. His book, divided into two parts, includes a thorough review of the basic literature written on medicine dating from (1) 2000 B.C. in the Hsin Dynasty through (2) Chou Dynasty 1122-255 B.C.—the initial reference to the Yin-Yang principle and the five elements and the use of acupuncture and moxibustion in medicine; (3) Han Dynasty—era of origin of the yellow Emperor's classic of internal medicine and other medical classics up to the present day. He explains the suppression of the use of traditional medicine during the Republic of China, 1911-1949 and its revival and merger with Western medicine in the People's Republic of China, 1949 to date. The chapter on the principles of Yin and Yang and the five elements is brief probably due to the difficulty of interpretation of the Chinese texts.

The explanation of the interrelation of medicine and philosophy as the sociological background in the history of medicine in China omits the basic Chinese concept of food, health, and disease emphasized in Chinese folk medicine. The author makes an effort to create a foundation for understanding the interpretation of the Chinese classics to the Western reader.

The main portion of his book deals with the various modalities of medical treatment including exercise, massage, use of herbs, respiratory therapy and, primarily acupuncture. There is a rather detailed account of the technique of acupuncture and moxibustion. The quotations of conditions, diseases, and disorders treated and percentage of success have undoubtedly given impetus towards looking at acupuncture as a panacea of all ills. Much of the work would do well to be repeated in controlled studies to prove the authenticity. This is not to say acupuncture is not in great use today in China. Indeed, the merger of the traditional doctor, the acupuncturists and the Western physician in the People's Republic of China is a great boon to progress of medicine. It is recognized that there are only one-seventh the number of modern trained physicians to the number of traditional doctors and the total is insufficient to care for the health needs. New hospitals and clinics have been set up as well as a system of training medical assistants.

This book does give the reader a good general introduction to the traditional art of healing and its chief methods of treatment. There are suggested areas of research and an attempt at scientific explanation of the unscientific concepts. In summary, this is one of the better books written on the broad topic of Chinese medicine but lacks depth and scientific professionalism.

JANE F. LEE, MD

* * *

DAVIS-CHRISTOPHER TEXTBOOK OF SURGERY—Tenth Edition—Edited by David C. Sabiston, Jr., MD, James B. Duke Professor and Chairman, Department of Surgery, Duke University Medical Center, Durham, North Carolina. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1972. Single volume, 2,135 pages, $27.50 (Two volume set, $35.00).

Dr. Sabiston assembled a distinguished group of contributing authors, each a recognized authority in a specific field of surgery, and produced a 2,135-page surgical text which maintains the superb conciseness of the original and subsequent editions of Christopher's Textbook of Surgery. The format is based on fundamental biological principles related to surgery and the text is subtitled "The Biological Basis of Modern Surgical Practice." To quote Dr. Sabiston, "The fundamental roles of physiology, biochemistry, immunology, pharmacology, and pathology form the basis for discussion of the pathogenesis, diagnosis and management of each disorder." Following a brief history of surgery by Dr. Brieger, Francis Moore's chapter "Homeostasis: Body Changes in Trauma and Surgery," a synopsis of his text, "Metabolic Care of the Surgical Patient," is a very appropriate introduction. The text is concluded with a chapter, "The Surgeon," written by Loyal Davis. Between these introductory and concluding chapters the entire field of surgery is encompassed with appropriate annotated bibliographies making this an unexcelled text and reference for the student of surgery, medical student, intern, resident, practitioner or teacher.

LINDSAY C. GETZEN, MD

Refer to: Crandall BF, Sparkes RS: Prenatal diagnosis of genetic disorders by amniocentesis. Calif Med 119:1-6, Nov 1973

California Medicine
THE WESTERN JOURNAL OF MEDICINE

Prenatal Diagnosis of Genetic Disorders by Amniocentesis

BARBARA F. CRANDALL, MD, and ROBERT S. SPARKES, MD, *Los Angeles*

FOR THE PAST TEN YEARS amniocentesis in the last trimester has been used in the management of Rh incompatibility and to determine the sex of the fetus.[1,2] During the past three years, amniocentesis in the second trimester has developed into a valuable diagnostic technique for the prenatal diagnosis of chromosome abnormalities and certain metabolic disorders. Liberalization of therapeutic abortion laws has contributed to the acceptance of amniocentesis, and abortion of an affected fetus by the twentieth week of gestation. Although a number of genetic centers are performing amniocentesis, the experience of any one clinic has been small and for this reason we feel it expedient to report our experience with the first 100 prenatal diagnoses performed by the Medical Genetics Unit at the UCLA Center for the Health Sciences.

The generally accepted indications for amniocentesis are shown in Table 1. Although the risks inherent in this procedure appear to be small, we believe there should be specific indications for its use. In general, amniocentesis should be considered where there is a risk of about 1 percent or more of a serious diagnosable disorder in the fetus.

Materials and Methods

The prenatal diagnostic service at this center has been in existence for approximately three years. Patients are divided into two groups: (a) those in which amniocentesis is performed at this center

TABLE 1.—*Indications for Amniocentesis*

Category	*Reason*	*Risk*
Chromosome abnormality	Maternal age greater than 35 years*	1% or greater
	Previous child with Down's syndrome	1%
	Parents known translocation carriers	12%-50% for mother 4%-50% for father
	Previous child with chromosome abnormality (sporadic)	Less than 1%
	Multiple anomalies—undiagnosed	?
Sex-linked disorders		
a. Specific enzyme assay available	Hunter's, Fabry's, Lesch-Nyhan	50% of males
b. For sex only	Duchenne muscular dystrophy, hemophilia	50% of males
Autosomal recessive disorders	See Table 4	25%

*Although some authors believe the risk for a chromosome abnormality is about 1 percent when the mother reaches approximately age 40, the study of Lubs and Ruddle suggests this risk occurs with a maternal age of 35 to 39.

From the Departments of Pediatrics, Psychiatry and Medicine, University of California, Los Angeles, Center for the Health Sciences.

Submitted February 8, 1973.

This research supported in part by: California State Department of Mental Hygiene; Mental Retardation Program, NPI, UCLA; MCH-927 Interdisciplinary Training in Mental Retardation; HD-04612, Mental Retardation Research Center, UCLA; HD-0035, Research Training in Mental Retardation; HD-05615, Developmental Biology in Mental Retardation.

Reprint requests to: B. F. Crandall, MD, Department of Pediatrics, UCLA Center for the Health Sciences, Los Angeles, CA 90024.

(approximately two-thirds of our total); and (b) those in which amniocentesis is performed elsewhere (usually by an outside obstetrician) and cells are cultured and the results interpreted here (approximately one-third). Group "a" consists of 65 patients in whom amniocentesis was felt to be indicated, using the criteria in Table 1. Approximately 80 patients contacted us concerning amniocentesis, and the criteria were met in 81 percent of these. Pre-amniocentesis counselling included a discussion of the indications, the risks, and the possible need for a therapeutic abortion. If abortion was not acceptable, there was generally no reason to perform amniocentesis. Both groups of patients were asked to acknowledge their understanding of the procedure by signing an information form which also included their consent for amniocentesis. In both groups, cards were mailed to the delivering obstetrician after birth for details of the baby, including maturity, birthweight, congenital abnormalities, sex, and results of a physical examination. Approximately ten months later the baby was seen at UCLA for a physical examination and developmental study.

The aspiration of the amniotic fluid is usually performed as an out-patient procedure between 14 and 16 weeks of gestation, at which time there is approximately 250 ml of amniotic fluid present. We do not use ultrasound to localize the placenta; after infiltration with a local anesthetic, a 21 gauge spinal needle with a stylet is used to enter the amniotic cavity and approximately 15 to 20 ml of fluid is aspirated. Occasionally, when no fluid was obtained, the stylet was reinserted and the needle withdrawn and redirected. Patients rarely complained of any discomfort. The amniotic fluid was transferred directly to the laboratory for culture. Fluid drawn elsewhere usually reached us within 24 hours (including specimens from nearby states by airmail special delivery). Amniotic fluid may stand at room temperature for as long as 24 hours but if a longer period is expected to elapse, it may be refrigerated but not frozen. The fluid is divided into two centrifuge tubes and each spun at 1,200 rpm for ten minutes; the supernatant is centrifuged once more and then frozen. The cell pellets are re-suspended in Ham's F12 media containing 30 percent fetal calf serum with penicillin and streptomycin, transferred to Falcon flasks, and cultured for seven days in 5 percent CO_2 in air at 37°C. After this period of time the cultures are examined and the media changed every two or three days. When confluent, the cells are subcultured and are usually harvested approximately three days later, following exposure to colchicine ($10^{-7.5}$M) for the last 16 hours.

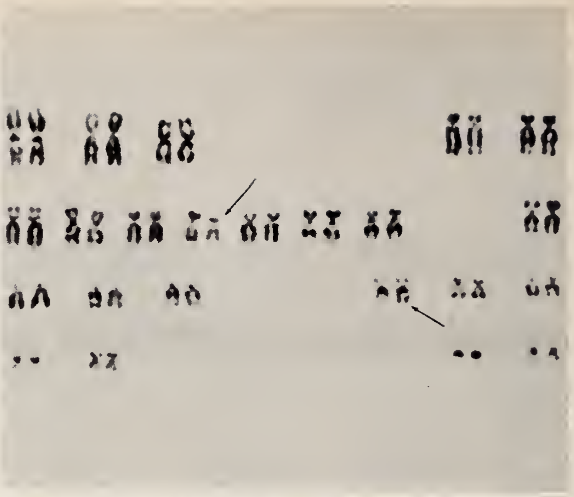

Figure 1.—This karyotype was prepared from amniotic fluid cells using a Giemsa differential banding technique. It demonstrates an apparent balanced translocation between the short arms of a No. 9 chromosome and the long arms of a No. 16 chromosome. The arrows denote an apparent balanced translocation between the No. 9 and No. 16 chromosome. Based on this finding, the fetus was not aborted.

Generally, we used routine chromosome preparations. However, in one case where the mother was a D-G translocation carrier, we used quinacrine fluorescence to confirm the D-G translocation Down's syndrome in the fetus. This abnormality was confirmed by further chromosome studies on the aborted fetus. In another case, where the mother was a known translocation carrier, both quinacrine fluorescence and Giemsa banding were used to determine that the fetus was also a balanced translocation carrier (Figure 1). These chromosome findings were confirmed after birth on the phenotypically normal child.

We foresee that similar or even routine studies with these special chromosome stains will arise in the future. We have not used quinacrine fluorescence to detect the Y chromatin body in interphase cells but we do routinely stain slides for the X-chromatin bodies. The latter studies are done on cultured cells and the results interpreted in conjunction with the karyotype.

Results

The reasons for amniocentesis in our series of 100 patients are shown in Table 2. We have divided our results into two groups: those for the procedures performed in 1970-1971, and for

TABLE 2.—*Reasons for Amniocentesis in 100 Patients*

Category	*Reason*	*No. of Patients*	*Results of Test*
Chromosome abnormality	Previous Down's	40	Normal
	Maternal age greater than 35 years	27	Normal
	Parent translocation carrier		
	Father	1	Normal
	Mother	5	3 Normal, 1 D-G Down's 1 translocation carrier
	Previous chromosome abnormality	4	Normal
	Multiple Down's in family	6	Normal
	Multiple anomalies	6	Normal
	Multiple abortions	1	Normal
TOTAL		90	
X-linked disease			
Hunter's		1	Male
Hemophilia		3	3 Males
Ocular albinism		1	Male
Nephrogenic diabetes insipidus		1	Female
TOTAL		6	
Metabolic abnormality			
Hurler's		2	Normal
TOTAL		2	
Miscellaneous			
Current immunosuppressive therapy		1	Normal
Abnormal sperm, previous infertility, and threatened abortion		1	Normal
TOTAL		2	

those in 1972. In our early studies, there were several instances where too little fluid was aspirated. In six cases, the obstetrician elected not to repeat the procedure (all done outside this center) and two patients were too advanced in pregnancy to allow for a repeat within the twentieth-week limit for a therapeutic abortion. In one case, amniocentesis was performed at 12 weeks and no fluid was obtained. In the second group (1972), there was much less hesitancy concerning the need for repeating amniocentesis. If there was no apparent cell growth by 10 to 14 days, we usually arranged for a second specimen of the amniotic fluid. In a number of instances, the cells of the first specimen started to grow at two to two and a half weeks. Eighty-two percent of the first fifty amniocenteses and 98 percent of the second were successful. The cells that attach and multiply appear to be of two types, round cells and fibroblasts; areas of proliferating cells may contain both types of cells or one may predominate.

The volume of the fluid aspirated varied from 4 ml to 30 ml (average 14 ml) and generally the chance of success diminished as the total fluid aspirated fell below 8 ml. There were exceptions and one rapidly growing culture resulted from withdrawal of only 6.5 ml of amniotic fluid. Recently we have requested 15-20 ml of fluid and usually obtain this amount without difficulty.

In 15 percent of the cases, the fluid was obviously bloody, evident in the fluid or in the cell pellet. In another 5 percent, red blood cells were only noted microscopically. In neither case did the blood appear to affect the success of the culture. Yeast contamination occurred in four cultures, but generally it was possible to control this with Fungizone®; one culture was sufficiently contaminated to be a failure. In five cases fibrin plugs were noted to be floating in the culture flasks but did not appear to affect the growth of the cells. In three instances, a piece of tissue of unknown source (probably placenta) was also present and care was taken to separate this from the rest of the cell pellet, and it was cultured in a separate flask. X-chromatin bodies from the two sources were analyzed separately and were always in agreement.

The time elapsing between submission of fluid and completion of the karyotype varied between 16 and 31 days (average, 24 days). We usually count 20 cells and karyotype two to four metaphases, depending on the quality of the first two karyotypes. The X-chromatin body is studied routinely in the cultured cells. In males, the num-

TABLE 3.—*Results of Amniocentesis*

	1970-1971 Series	*Percent*	*1972 Series*	*Percent*
No. of patients	52	..	48	..
No. successful on first attempt	41	79	43	90
No. repeated and successful	2	..	4	..
No. not repeated	9*	..	1	....
Total successful first and second attempt	43	83	47	98

*Includes one patient from whom no fluid was obtained.

ber of X-chromatin bodies was generally 0 to 1 percent but occasionally reached 4 percent. In females, the number usually varied between 30 and 50 percent; however, we had one each of 7 percent, 17 percent, and 18 percent. Polyploidy was variable; sometimes it was observed in 10 to 15 percent of cells examined but usually in no more than 1 to 2 percent.

Three of our patients have had amniocentesis in each of two successive pregnancies. In one instance, this was because of maternal age and in two because the mothers were D-G translocation carriers.

Two patients had "spontaneous" abortion following amniocentesis. One of them was a hemophilia carrier; no fluid was obtained at amniocentesis and she aborted within 12 hours of the procedure. The second patient aborted four weeks after amniocentesis and was found to have a bicornuate uterus. There were five therapeutic abortions, one for a D-G translocation Down's syndrome, three for sex when the fetus was male and the suspected disorder was sex-linked (hemophilia, Hunter's syndrome, ocular albinism), and one electively despite finding normal fetal cells in a patient who had had a previous child with Hurler's syndrome. There was one reported sex difference in a therapeutically aborted fetus. The fluid was aspirated elsewhere and a 46,XX complement was found in the amniotic fluid cells and confirmed by two subsequent subcultures. The 20-week fetus was aborted and was reported as male by superficial external examination only. There were three premature (by dates) babies, one of whom weighed 6 pounds and all of whom are developing normally. Birthweights varied from 6 pounds to 9 pounds 15 ounces. One baby was born with a cleft lip and palate; chromosome studies were repeated postnatally and also found to be normal. Seventy-seven babies have been delivered, all were examined at birth and this was the only abnormality reported. Of the 18 infants examined at ten months, all have been normal and developmental studies showed intelligence quotient varying between 90 and 122. One patient aborted spontaneously between her appointment and her first contact with us. No patients reported loss of amniotic fluid through the vagina following amniocentesis.

Discussion

The ability to make a prenatal diagnosis of certain genetic disorders has offered a new dimension to genetic counselling and preventive medicine. Previously, it was possible to tell a couple the statistical risk of abnormality in a child they conceived, such as a 1:100 chance of having a child with a chromosomal anomaly (for example, Down's syndrome) or a 1:4 chance for autosomal recessive traits. With amniocentesis, it is possible to modify these risks to either zero or 100 percent for chromosome anomalies and several inborn errors of metabolism. The preventive aspect focuses on the therapeutic abortion of an affected fetus.

The largest proportion of our patients had amniocentesis to detect a chromosome abnormality. The risk that a woman of 20 years of age will have a child with Down's syndrome is about 1 in 2,000 births; however, that risk becomes approximately 1 in 40 births when the mother is 45 years of age. As approximately 55 percent of all Down's syndrome children are born to mothers over age 35, it should be possible to halve the incidence of this syndrome by monitoring all pregnancies in this age group with amniocentesis. Although a maternal age greater than 35 years would seem to be the most frequently expected indication for amniocentesis, this was the reason for only seven of our first 50 studies and for only 20 of our second 50 cases. The reason for amniocentesis in 22 instances in our first 50 cases and for 18 in the second 50 was a previous child with Down's syndrome. We expect maternal age to be an increasingly common reason for amniocentesis. For a couple who have had one child with trisomy 21, the risk for another is about 1 percent. Where either parent is a known translocation carrier, the risk for a child with a chromosome abnormality becomes much higher and probably varies between 12 and 50 percent when the mother carries the translocation; the higher figure of 50 percent might apply if all conceptuses survive. The risk appears to be generally

TABLE 4.—*Inborn Errors of Metabolism Diagnosed in Amniotic Cells*

Disease	*Enzyme Defect*
Fabry's disease	α-galactosidase A
Galactosemia	Galactose-1-phosphate uridyltransferase
Gaucher's disease	Acid β-glucosidase
Glycogen storage disease type 2 (Pompe's disease)	α-glucosidase (lysosomal)
GM_2 gangliosidosis type 2 (Sandhoff's disease)	Hexosaminidase A,B
GM_2 gangliosidosis type 3 (Tay-Sachs disease)	Hexosaminidase A
Krabbe's disease	Galactosylceramide β-galactosidase
Lesch-Nyhan syndrome	Hypoxanthine-guanine phosphoribosyltransferase
Lysosomal acid phosphatase deficiency	Lysosomal acid phosphatase
Maple syrup urine disease	Branched-chain keto acid decarboxylase
Metachromatic leukodystrophy	Sulfatide sulfatase
Mucopolysaccharidoses	
1. Hurler's syndrome	α-L-iduronidase
2. Hunter's syndrome	β-galactosidase (?)
Niemann-Pick disease	Sphingomyelinase

lower where the father is the translocation carrier, but in both situations the risks may vary with the chromosomes involved. Generally, we recommend amniocentesis when a chromosome abnormality in a previous child may be suspected because of multiple anomalies, even without a chromosome analysis. Rarely, pedigrees reveal multiple cases of Down's syndrome, but when they do we consider this to be a valid indication for amniocentesis.

In sex-linked disorders, amniocentesis may be used for specific biochemical studies where these can be identified directly and for sex alone where the mother is a probable carrier of a disorder that cannot be specifically determined. In X-linked recessive disorders (for example, hemophilia) only males will be affected. Fifty percent of the aborted males would be expected to have developed the disease and the other 50 percent to have been normal.

Metabolic disorders that have been identified in amniotic cells are indicated in Table 4. Those in which the disease is potentially detectable, based on the manifestation of the defect in the fibroblasts of affected persons, are summarized in recent publications[4-6] and the list continues to grow. Usually, the need for amniocentesis becomes evident after an older child develops the disorder, but in Tay-Sachs disease this can be avoided by studies on both parents to identify carriers.

There are important differences between the prenatal diagnosis of chromosome problems when the same test can detect any chromosome change on the one hand, and on the other the inborn errors of metabolism where each disorder requires a specific biochemical assay. In addition, while amniotic cells are usually representative of all fetal cells in their chromosome complement, metabolic disorders may only be expressed in specialized tissues such as red blood cells or liver cells and not in amniotic fluid cells. Nevertheless, progressively increasing numbers of the inborn errors are being detected in amniotic cells. There is a tendency at present for a single laboratory to carry out a few of these tests and to turn to another laboratory for analyses that it cannot do itself. As with the chromosome studies, there is general agreement that most of the biochemical studies should be performed on cultured amniotic cells and not on the amniotic fluid or on uncultured cells. At present, most of these biochemical studies require a moderate number of cells and a month or longer may elapse before sufficient cells are cultured. Attempts to develop microtechniques are proceeding.

As it has with others,[7,8] experience has increased our success in culturing amniotic cells. At first the possible effects of removing even 5 to 10 ml of amniotic fluid from the uterus caused misgivings among those performing the procedure. Frequently in the earlier cases a minimal volume of fluid was aspirated and if the cells failed to grow in culture, the procedure was rarely repeated. The success rate in our second group (1972) increased to 90 percent with the first aspiration and this improvement is continuing. We have had no "spontaneous" abortions following amniocentesis in the second group of 50 cases. The proportion of second trimester abortions in patients without amniocentesis is not known, but Robinson et al[9] reported on 100 cases of amniocentesis and noted 11 patients who aborted between the time of making their appointment and the procedure. We have had one patient with a similar experience. Fetal damage has not been noted in any of our patients or in reports from other centers.

It seems certain that amniocentesis will be used more extensively with time, especially as its apparent safety becomes more evident. The number of metabolic errors detectable is expected to increase, and continued improvement in cytogenetic techniques should identify persons who are carrying more subtle chromosome changes. These factors, coupled with a greater awareness of the availability of amniocentesis, will very likely lead to an increased demand for the test.

In the majority of cases amniocentesis does not lead to a decision for therapeutic abortion, and it is important therefore to consider the possible effects of the procedure on the fetus. At present, there is no evidence of any adverse effect but appropriate studies are in progress in this and other centers to examine this possibility. Finally, it should be emphasized that the test only gives information concerning the specific abnormality being investigated and in no way guarantees that the child to be born will be normal, for there are still the usual risks of other congenital problems. However, the use of radio-opaque dyes and the development of a safe amnioscope will add another dimension to prenatal diagnosis in the future, particularly in detecting congenital malformations not associated with a chromosome abnormality.

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Treatment of Shock Caused by Bacterial Infections

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Bacteremia caused by Gram-negative enteric organisms accounts for the majority of instances of shock complicating bacterial infection. Control of the infection and maintenance of normal blood volume constitute the primary considerations in immediate treatment. The use of three or four doses of corticosteroid agent over a period of 24 hours is regarded as advantageous for routine treatment. Conservative and selective use of isoproterenol and phentolamine are justified for management of patients who do not respond to the administration of bactericidal drugs and volume repletion. Levarterenol and metaraminol are rarely indicated. Intravascular coagulation complicated by bleeding diathesis may serve as an indication for anticoagulation.

With more effective management of the hemodynamic defects, patients are now more likely to survive the shock state only to develop a fatal form of pulmonary failure which is yet poorly understood. Close attention to respiratory management is therefore advised.

WHEN CIRCULATORY SHOCK occurs as a complication of a severe infection, the condition is described as septic shock. Gram-negative enteric bacilli (Table 1) account for a majority of cases of bacterial shock. However, Gram-positive cocci, including the pneumococci, Staphylococcus aureus and Streptococcus hemolyticus, are the causes of infections which account for bacterial shock in a minority of cases. In addition, systemic infection due to meningococci, Clostridia and infections caused by organisms other than bacteria, including viruses, Rickettsia, and fungi are occasionally complicated by shock.

In this review, our primary focus is on the pathophysiologic and clinical features and the rationale of treatment of shock when it occurs as a complication of systemic infection due to Gram-negative enteric organisms. Both the age and the sex of the patient play important parts. Bacteremia is very rarely complicated by shock before the age of 40 except in young women during pregnancy or in infants in the neonatal period. If patients with septic abortion are excluded, the condition is approximately twice as frequent in men as in women. This reflects the higher incidence of urinary tract infection primarily due to diseases of the prostate

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TABLE 1.—*Gram-Negative Species of Enteric Bacilli Which Most Commonly Cause Bacterial Shock*

Escherichia coli
Aerobacter-Klebsiella
  (Aerobacter aerogenes, Klebsiella pneumonia-Friedlander)
Proteus
Paracolon bacilli
Pseudomonas pyocyanea
Salmonella

gland in older men. Diabetes, chronic liver disease, and blood dyscrasias predispose to bacteremia and shock.[1]

In most patients, a traumatic event, especially instrumentation, initiates bacteremia and shock. Surgical operation or instrumentation of the genitourinary tract is the most common cause. Other causes include operation on the gastrointestinal tract, severe burns, and manipulation of infected wounds. A disproportionately high incidence of Gram-negative sepsis also is observed in patients who receive immunosuppressive drugs, radiotherapy and prolonged treatment with antimetabolites for the management of neoplastic diseases. Prolonged treatment with corticosteroid hormones also predisposes to bacteremia and shock.[1,2]

Pathophysiology

The mechanisms which account for shock as a complication of infection reflect the biological difference between the causative organisms.[3] The specific bacteriological cause of the infection is therefore a primary consideration not only for purposes of antimicrobial therapy but also for better understanding of the mechanism of shock and its management in an individual case.[4]

In shock states caused by Gram-positive organisms, Rickettsia and viruses, vascular permeability is often increased so that there is a loss of fluid from the intravascular compartment. This, together with vasodilation as part of an inflammatory response involving the arterial resistance vessels, accounts for hypotension.

When shock occurs as a complication of bacteremia due to Gram-negative enteric bacteria, a more complex sequence of disturbances is involved. The patient may present with hypotension and warm extremities, the so-called interval of "hot shock." Arterial vasodilation usually occurs during the pyrogenic phase of the infection together with a pronounced increase in body temperature, hyperventilation with an element of respiratory alkalosis, and an increase in pulse pressure and cardiac output.[5-7] This is followed by clinical changes that are more typical of shock states, including cold extremities, oliguria, and arterial vasoconstriction with a relatively small pulse pressure. The cardiac output is reduced and the peripheral arterial resistance is usually increased.

The heart does not appear to be at fault. The best explanation for bacterial shock caused by Gram-negative enteric organisms is a redistribution of the blood volume. A substantial portion of the total volume appears to be pooled in the venous capacitance bed and hence the "effective circulating blood volume" is decreased. This results in a reduction in the volume of blood returned to the heart and, consequently, the lowering of cardiac output. Clinical signs of perfusion failure appear, including decreased mental alertness and stupor due to decreased cerebral blood flow, oliguria due to decreased renal blood flow, and cool and sometimes cyanotic skin particularly in the extremities, the tip of the nose and the ear lobes due to a reduction in skin blood flow. The blood pH is reduced and lactic acid accumulates in tissues and fluid spaces because the blood flow to muscle and viscera is not sufficient for support of normal aerobic metabolism.[3,4]

In experimental animals, shock may be induced by the injection of purified endotoxin which is a protein lipopolysaccharide complex extracted from Gram-negative organisms. It is the polysaccharide component of endotoxin that is the probable cause of the hemodynamic disturbance.

More recently, intravascular coagulation has been implicated as part of the shock syndrome. The extent to which this represents a specific phenomenon due to the action of the polysaccharide or whether it is largely due to the stagnation which occurs when blood flow is greatly reduced, is not yet clear.

Clinical Features

Typically, bacteremia due to Gram-negative enteric bacteria is heralded by a shaking chill followed by a rapid rise in temperature to levels exceeding 39°C (102.2°F). These events most often occur between two and 24 hours after pelvic surgical procedures or mechanical manipulation of the genitourinary tract. Because the skin is warm and dry during the early stage of shock, the physician may not suspect that the blood pressure has fallen. An early clue to shock may be the relatively abrupt alteration in personality and inappropriate behavior due to a reduction in cerebral blood flow. The cause becomes apparent as soon as the patient's blood pressure is ascertained. In a series of 169 cases of bacterial shock, the average arterial pressure fell from 138/78 to 70/36 mm of mercury.[1] As the hemodynamic defect becomes more profound, the skin becomes pale, cool and moist. Approximately one half of the patients present with gastrointestinal signs, including hyperperistalsis followed by vomiting and diarrhea, often with green and sometimes bloody stools with a characteristic "laundry room" odor.

A typical laboratory finding during the very early stages of shock is an abrupt reduction in the white blood cell count with primary reduction in the polymorphonuclear cells. Later, there is an overall increase in white cells usually to levels exceeding 20,000 cells per cubic centimeter with a decided rise in polymorphonuclear cells. Increases in serum glutamic oxalic transaminase, serum glutamic pyruvic transminase, and lactic dehydrogenase reflect cellular injury due to perfusion failure. Elevation of blood sugar reflects secretion of increased amounts of catecholamines from the adrenal medulla. Since urine flow is decreased, the renal clearance of amylase also is reduced and serum amylase may be considerably elevated in the absence of pancreatic injury. The electrocardiographic findings must be interpreted with great caution since T wave and ST segment abnormalities are not unusual in older patients after the onset of shock regardless of cause. These electrocardiographic changes are especially pronounced in patients who have coexisting coronary artery disease.

Rationale of Management

The prompt administration of antibiotics and attention to the hemodynamic status of the patient during the interval of decompensation constitute the primary aims of treatment.[8]

Selection of Antibiotic

The period from onset of shock until death is short, typically less than 48 hours. This interval has important therapeutic implications. Appropriate antibiotic treatment may triple the chances for survival.[1] However, the opportunity for such benefit will be missed if the clinician awaits the results of sensitivity studies before initiating antibiotic therapy. In instances in which pre-existing infection in the urinary tract, a wound, or another site has been recognized and the organism previously recovered, it may be reasonably assumed that the same organism accounts for bacteremia. When the results of *in vitro* antibiotic sensitivity studies on such organisms are available, antibiotics are best selected accordingly.[3]

Bacterial populations and the spectrum of antibiotic sensitivities vary from hospital to hospital and change over time within the same hospital environment. Antibiotic sensitivity tests are helpful, not only for the individual patient but also to characterize the spectrum of bacterial sensitivity in a particular institution. Before an antibiotic is administered to a patient, three specimens of blood for culture should be taken in sequence with a single vein puncture or from the central venous catheter. The specimens are labeled 1, 2, and 3. This identification is helpful since the first specimen is more likely to contain a contaminant if organisms are not recovered from the second and third samples. Antibiotic treatment is then begun on an empirical basis.

Corticosteroid Drugs

In some situations, bactericidal drugs may potentiate shock when large amounts of endotoxin are liberated from the cell wall of the dead bacteria. There is evidence that such deterimental effects of endotoxins may be prevented by the administration of pharmacological doses of corticosteroids together with the antibiotic.[2] In these circumstances, the corticosteroid acts as a drug rather than as hormone replacement since adrenal cortical insufficiency has not been demonstrated to be the cause of the shock state. Corticosteroids, in amounts which may be 50 times greater than those required for adrenal replacement, suppress systemic reactions to endotoxin, control fever, and tend to prevent the nonspecific injury of cell structures. They also increase cardiac output and decrease peripheral arterial resistance. These effects are directly opposite to the hemodynamic defects that are observed during bacterial shock in patients and in some experimental animals following the administration of the bacterial endotoxin.

Significantly higher survival has been reported by us in patients who received large doses of synthetic corticosteroid drugs.[1,9] Similar observations were made by Christy,[10] Melnick,[11] and Motsay.[12] However, the present use of this therapy is based on extrapolations from animal experiments and retrospective comparisons of survival of patients treated with and without corticosteroids. In the absence of controlled studies, the therapeutic efficacy of costicosteroid analogs for treatment of patients with bacterial shock is not proven.

Volume Expansion

Considerable quantities of fluid often are sequestered at a site of inflammation or are lost because of fever, vomiting, or diarrhea. Since shock is greatly intensified when intravascular volume is depleted, fluid replacement may be an important component of therapy. Monitoring of the central venous pressure with a catheter in the vena cava or right atrium is most helpful for judging the capacity of the heart to handle the volumes of fluid which are administered.[13] If the central venous pressure is not in excess of 16 cm of water, fluid therapy is best attempted. The response to fluid may be judged from state of mental awareness, blood pressure, urine output, measurement of arterial blood pH, PCO_2, and PO_2 and measurement of changes in the central venous pressure. A rise in central venous pressure of more than 5 cm of water in response to a fluid challenge of 100 ml suggests that the heart is unable to handle additional fluid loads.

With the availability of flow-directed pulmonary artery catheters which may be inserted at the bedside without fluoroscopic control, the clinician is provided with a practical means for routine monitoring of pulmonary artery and wedged pulmonary artery pressures.[14] These measurements and especially wedged pulmonary artery pressure or pulmonary diastolic pressure constitute more precise and reliable indicators of left atrial and left ventricular filling pressure. Sudden increases in wedged pulmonary artery pressure or pulmonary diastolic pressure of more than 8 mm of mercury, or increases to levels exceeding 22 mm of mercury during volume loading, reflect critical levels of left ventricular competence. Even when the blood volume is not reduced, the infusion of fluids usually improves cardiac output as long as the pulmonary or central venous pressures do not indicate overload.

A 5 percent solution of normal human albumin is an ideal volume expander. Whole blood should be administered only when indicated. Our group favors a combination of isotonic sodium chloride with 5 percent normal human serum albumin, USP or plasma protein fraction, USP. While macromolecular dextrans (molecular weight 70,000 to 80,000) gelatin solutions, and hydroxyethyl starches (polymers of sorghum corn starch) have been employed as volume expanders, we do not favor their routine use because of adverse reactions, including increased risk of defects in blood clotting, interference with subsequent crossmatch of blood, and hypersensitivity reactions.

Alkalinization

Although acidosis frequently accompanies bacterial shock, the rationale of administering sodium bicarbonate for its reversal is questioned. Acidosis is due to failure of effective tissue perfusion rather than to a deficit of sodium ion. However, for purposes of cardiac resuscitation, reversal of metabolic acidosis by administration of between 40 and 160 mEq of sodium bicarbonate may be warranted, but effects on blood pH and osmolality should be monitored.[15]

Anticoagulation

There is justification for the administration of heparin to patients who present with signs of gross bleeding due to consumption coagulapathy, presumably due to intravascular coagulation. This treatment should be reserved for the exceptional case. It is a relatively more common complication during meningococcemia.[16]

Vasopressor and Vasodilator Drugs

The effectiveness of various vasoactive drugs for the treatment of bacterial shock has been critically examined, and particularly the indications for the use of vasopressor agents. There is general agreement that neither levarterenol (Levophed®) nor metaraminol (Aramine®) is indicated for routine treatment. To the contrary, there is evidence that they increase peripheral vasoconstriction and further compromise effective blood flow. In instances in which there is concurrent myocardial failure due to coronary insufficiency, there may be an indication for temporary increase in perfusion pressure and consequent increase in coronary blood flow. However, the effectiveness of their use even for this purpose is not fully established.

If the signs of peripheral vasoconstriction are not improved by the use of volume expanders, the possibility that isoproterenol (Isuprel®), a beta adrenergic stimulant, or alpha adrenergic blocking agents such as phenoxybenzamine (Dibenzyline®) or phentolamine (Regitine®), which serve to dilate arterial vessels, might be effective has been investigated with some promising results. Phenoxybenzamine is not currently available as an approved drug. Isoproterenol, which is a

TABLE 2.—*Suggested Doses of Antimicrobial Agents with Adjustments for Patients with Renal Failure*[*]

Agent	*Loading dose*	*Subsequent single dose, interval, and route*	*Adjusted interval between single doses*	
			Anuria[†]	*Uremia*[‡]
Gentamycin sulfate	2.5 mg/kg	1.5 mg/kg, q 8 h, I.M.	3-4 days	2 days
Kanamycin sulfate	7.5 mg/kg	2.5 mg/kg, q 6 h, I.M.	3-4 days	2 days
Streptomycin	15 mg/kg	7.5 mg/kg, q 6 h, I.M.	3-4 days	2 days
Colistimethate sodium	5 mg/kg	2.5 mg/kg, q 12 h, I.M.	3-4 days	2 days
Polymyxin B sulfate	2.5 mg/kg	0.6 mg/kg, q 6 h, I.M.	3-4 days	2 days
Tetracycline	1.0 gm	0.25 gm, q 4 h, I.V.	3-4 days	2 days
Chloramphenicol	1.0 gm	0.5 gm[§], q 4 h, I.V.	6 hours	6 hours
Ampicillin	2.0 gm	1.0 gm, q 4 h, I.V.	12 hours	6 hours
Cephalothin sodium	3.0 gm	1.5 gm, q 4 h, I.V.	24 hours	12 hours

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[*] Modified from Barnett and Sanford.[8]

[†] Creatinine clearance less than or equal to 10 ml/minute.

[‡] Creatinine clearance greater than 10 ml/minute.

[§] Reduce dose in patients with severe liver disease.

I.M. = deep intramuscular injection.

I.V. = slow intravenous injection or infusion over 3 to 15 minutes.

potent cardiac stimulant, also carries the potential risk of tachycardia and cardiac arrhythmias. Both drugs may cause further decline in blood pressure. However, with progressive perfusion failure, the temporary use of these agents may be justified. We prefer the use of phentolamine inasmuch as isoproterenol acts not only as a cardiac but as a more general metabolic stimulant. It thereby increases the demands for tissue oxygen and hence the need for increased blood flow at the very time when blood flow is already markedly curtailed. In instances of congestive heart failure, and particularly when this is elicited by a fluid challenge, there is good indication for the administration of cardiac glycosides, either lanatoside (Cedilanid®) or digoxin (Lanoxin®).

General

The more general principles of immediate care inherent in the "VIP" approach to the bedside management of shock—that is, ventilation, infusion, and pumping—are advised.[17] Initial and continuing attention to ventilation is an essential part of routine treatment since more effective management often permits the patient to survive shock only to succumb subsequently to respiratory failure, the so-called "shock lung" syndrome.

In the management of bacterial shock, surgical treatment may be indicated for control of the bacterial infection. It is essential that abcesses be promptly drained and that grossly infected tissues be removed. For instance, hysterectomy may be life-saving in instances of shock complicating septic abortion, and surgical drainage of a large intraabdominal abscess is essential if antibiotics are to control the infection.

Specific Management

Antibiotics

For empirical therapy, gentamycin (Garamycin®) is now the drug of choice in our center. It is administered by intramuscular injection in amounts of 1.5 mg per kg of body weight every eight hours. On the basis of *in vitro* studies, it is effective against more than 90 percent of common strains of Gram-negative enteric organisms with the exception of proteus species, for which *in vitro* sensitivity is approximately 75 percent. This bactericidal agent has both vestibular and ototoxicity, especially when there is concurrent renal failure. Its nephrotoxicity is probably a lesser problem. Gentamycin is also highly effective against Staphylococcus aureus and therefore provides a special advantage, especially when Gram-negative enteric and staphylococcus infections coexist. Kanamycin (Kantrex®) is the drug of second choice. After a loading dose of 7.5 mg per kg of body weight, 2.5 mg per kg may be administered by deep intramuscular injection at six-hour intervals. We do not currently advise the use of these agents by the intravenous route.

When urine output is reduced to less than 800 ml a day, the dose of both gentamycin and kanamycin are correspondingly reduced. If urine output is 400 ml per 24 hours or less, the dose is reduced to one half, and if the urine output is 200 ml per 24 hours, the dosage is reduced to one fourth of the standard dose. For the use of these and other commonly used antibiotics for treatment of patients who have chronic renal disease, additional guidelines are provided in Table 2.[5,18]

In instances in which gentamycin is administered, no additional agent is usually indicated. However, kanamycin is preferably used together with chloramphenicol (Chloromycetin®) during the interval before results of bacterial studies are available. Chloramphenicol is administered in amounts of 1.0 gram diluted in 50 ml of saline solution and is injected into a central vein over a period of three to fifteen minutes. A dose of 1.0 gram is repeated every six hours. As an alternative to chloramphenicol, cephalothin (Keflin®) may be infused intravenously in amounts of 1.5 gram every four hours.

If the infecting organism is known to be a penicillin-sensitive Proteus species, or if there is a concomitant infection with Gram-positive organisms, we advise ampicillin in amounts ranging from 6 to 12 grams per day. Penicillin administered by intravenous infusion in a dose of 12.5 grams (20 million units) daily may also be employed. In patients with acute renal failure, the sodium salt is preferred, since each one million units of potassium penicillin contains 1.67 mEq of potassium.

In infections due to Pseudomonas, a new semisynthetic penicillin, carbenicillin, is likely to be effective following infusion of between 20 and 40 grams per day. Infections due to klebsiella aerobacter which are resistant to kanamycin and chloramphenicol may be treated with intramuscular injections of colistimethate (Coly-Mycin®) or polymixin B (Aerosporin®) in amounts shown in Table 2. However, gentamycin is usually very effective. The use of tetracycline drugs, which are bacteriostatic, is reserved for instances in which there is clear superiority over bactericidal agents on the basis of *in vitro* sensitivity studies.

The administration of antibiotics one or two days before instrumentation or surgical operation has proven relatively ineffective in preventing bacteremia in shock patients with low grade urinary tract infections. We prefer that antibiotics be withheld for a period of one week before operation. If this is not feasible, soluble chemotherapeutic drugs such as sulfonamide or nitrofuran may be used before operation, but antibiotics should be withheld until specific indication arises.

Corticosteroid Agents

Potent synthetic cortisone analogs are selected since animal experiments reveal lesser toxicity when these steroids are administered in massive doses. An initial intravenous injection of dexamethasone phosphate (Decadron®) in an amount of 40 mg, is followed by injections of 20 mg at intervals of four to six hours. In most cases, only three or four injections are needed. Methylprednisolone succinate (Solu-Medrol®) may be used instead in a dose of 200 mg followed by doses of 100 mg at four-hour to six-hour intervals. Lillehei recommends even higher doses, namely 6 mg per kg of dexamethasone and 30 mg per kg of methylprednisolone.[19] However, we are not aware of objective data demonstrating increased therapeutic efficacy with these larger doses. Treatment is stopped abruptly once shock has been reversed. Suppression of adrenal cortical function is not a problem when treatment is limited to a one or two day period and no weaning is required. Hemorrhage from the upper gastrointestinal tract is a specific and not infrequent complication of this type of therapy and corticosteroid treatment should be immediately discontinued if there is evidence of bleeding from the upper gastrointestinal tract.

Vasoactive Drugs

The so-called vasopressor drugs should be used rarely and judiciously when cardiac complications supervene and only in doses which raise blood pressure just enough to maintain urine flow, preserve mentation and minimize electrocardiographic evidence of myocardial ischemia. The desirable blood pressure level is usually 20 to 30 mm below "normal" systolic pressure. The preferred pressor drug is metaraminol (Aramine). Since excessive vasoconstriction may further compromise effective blood flow and increases the workload on the heart, care is taken to minimize dosage.

Metaraminol is used in amounts of 200 to 500 mg diluted in one liter of physiological salt solution or 5 percent glucose. It is administered by continuous intravenous infusion. Although metaraminol is preferred because it causes no local ischemic injury to tissues if the needle or catheter is dislodged from a vein, levarterenol may be employed with almost equal safety in amounts of 16 mg per liter of fluid, provided 10 mg of phentolamine mesylate (Regitine) is added to each liter of fluid.

When other measures fail, a cautious trial of isoproterenol hydrochloride (Isuprel) may be justified after care has been taken to assure volume repletion. A striking increase in cardiac output is often observed during infusion of between 0.20 and 25 micrograms of isoproterenol per minute. We prefer phentolamine for these purposes after volume has been expanded and particularly in instances in which clinical signs of severe vasoconstriction are unaltered by more routine treatment. Phentolamine may be infused in amounts ranging from 0.1 to 2 mg per minute over a period of 20 minutes. Following infusion of phentolamine, a decline in blood pressure may be promptly reversed by administration of additional quantities of fluid, preferably equal parts of 5 percent human serum albumin and physiological salt solution.

Adjunctive Treatment

Fever may be controlled with a cooling blanket. However, there is no evidence that depression of temperature to subnormal levels is advantageous. Chilling should be avoided, since it greatly increases the requirements for oxygen. Close attention to respiratory function is mandatory. In addition to the routine use of oxygen, the physician should be prepared to institute endotracheal intubation, mechanical ventilation, and tracheostomy. For treatment of intravascular coagulation, 5,000 international units of heparin is injected intravenously every four hours, guided by periodic measurements of blood clotting.

Conclusions

Bacteremia caused by Gram-negative enteric organisms accounts for the majority of instances of shock complicating bacterial infection. Control of the infection and maintenance of normal blood volume constitute the primary considerations in immediate treatment. The use of three or four doses of corticosteroid agent over a period of 24 hours is regarded by our group as advantageous for routine treatment. Conservative and selective use of isoproterenol and phentolamine are justified for management of patients who do not respond to the administration of bactericidal drugs and volume repletion. Levarterenol and metaraminol are rarely indicated. Intravascular coagulation complicated by bleeding diathesis may serve as an indication for anticoagulation. With more effective management of the hemodynamic defects, patients are now more likely to survive the shock state only to develop a fatal form of pulmonary failure which as yet is poorly understood. Close attention to respiratory management is therefore advised.

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Specialty Conference

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Inflammatory Bowel Disease

A Symposium

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PART I

The Radiological Differential Diagnosis Between Ulcerative and Granulomatous (Crohn's) Colitis

GERALD W. FRIEDLAND, MD, *Stanford*

FOR THE clinician or radiologist who first sees a patient with ulcerative colitis or Crohn's disease, the radiological differential diagnosis between these two conditions may be extremely difficult. In reviewing the early films of patients who were subsequently referred to us at a more advanced stage, we have frequently found that the early films were inconclusive. We completely agree with the statement made by Stanley et al:[5]

"In less severe disease, the radiological distinction between the two conditions is likely to be less precise. This is especially so with ulcerative colitis since the diagnostic signs are seen mainly in advanced disease. It is not quite so true of Crohn's disease since the characteristic signs of the mucosal lesion are frequently seen when the disease only involves a small area of bowel. In the absence of the characteristic signs, the radiological diagnosis becomes one of nonspecific colitis. Difficulty arises particularly in patients with distal symmetrical protocolitis with superficial ulceration. In this situation the more likely diagnosis is ulcerative colitis, but some cases will progress to florid Crohn's disease."

We disagree, however, with the statement which Margulis et al[3] have made: "It should be noted, however, that the frequent overlap of roentgen signs in our series may not confront the radiologist in the community. Patients referred to a University Medical Center usually have more severe and advanced colon disease, requiring colectomy in many instances."

In our experience, it is the *early* cases that are

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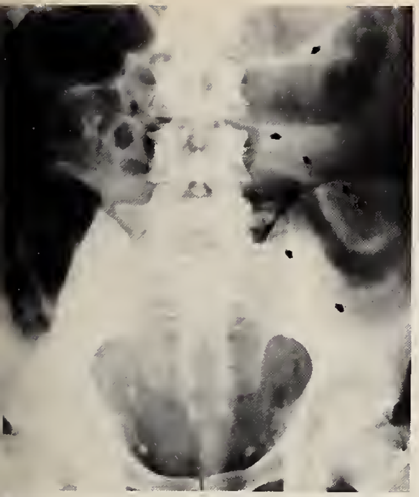

igure 1.—Plain supine abdominal radiograph n a patient with granulomatous colitis. Note he thick-walled loop of sigmoid colon (arrows). ecause the fat line, seen on the original radioraph, did not reproduce well on the photoraph, it was accentuated by outlining it in encil. Several dilated loops of small bowel are lso present (arrows).

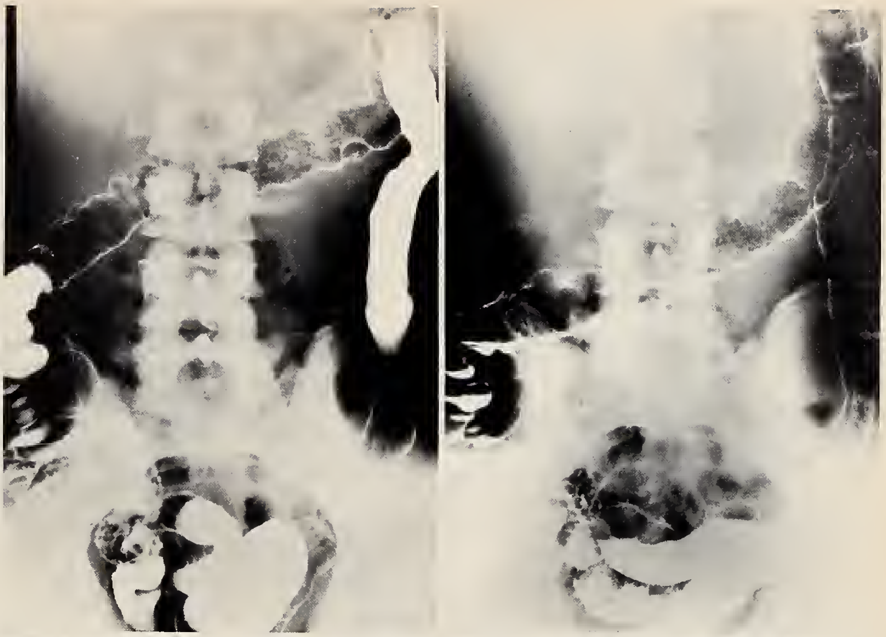

Figure 2.—The St. Mark's Hospital instant enema ("jiffy enema"). **Left,** prone. **Right,** upright radiographs. The entire colon (except the cecum) is diseased, and demonstrates haustral abnormalities and a fine, granular, textured mucosal surface, characteristic of ulcerative colitis.

hard to tell apart, *not* the more advanced cases.

This paper will discuss the two diseases in terms of how best to search for them. But the search will depend on three factors; (1) the type of barium used, (2) the radiographic factors involved, and (3) the barium enema technique. The preliminary radiograph, furthermore, may be of some help in the differential diagnosis.

Preliminary Radiograph

Although barium studies will usually provide many more clues, the thick wall characteristic of granulomatous colitis will sometimes be evident on a plain abdominal radiograph (Figure 1). The thick wall is seen because one of the characteristic phenomena that occur in granulomatous colitis is the so-called "creeping fat" which encircles the bowel. Because of this thick fat layer, a lucent line appears on the radiograph which marks the outer wall of the gut. Gas within the lumen demarcates the inner wall of the gut. The wall thickness can be seen between the intraluminal gas and the outer fat stripe.

Barium Enema

Barium Enema Techniques

Before discussing the radiographic findings on barium enemas, it will be necessary to discuss the types of barium enema examinations that are available. At present in the United States two methods are usually used. By far the most commonly used method is the dilute barium enema, high kilovolt examination. In this technique, the colon is filled with barium, diluted to 15 to 18 percent weight-volume. The radiographs are exposed at 110 to 120 kilovolts. The object of this method is to be able to see through the barium in the lumen of the gut, so that small polypoid lesions will not be obscured by the dense barium. The second method is the barium-air contrast enema. This method has largely fallen into disrepute in the United States because it is claimed that the patient experiences more discomfort and that the colon requires better preparation than for a conventional enema. In addition, success is not always insured, and if any technical difficulties arise during the examination so that it becomes uninterpretable, it has to be repeated on another day. A poorer dilute barium, high kilovolt examination, on the other hand, can usually be salvaged. Following evacuation of the barium, it is frequently possible to refill the patient on the same day to obtain an adequate examination. The biggest reason the barium-air contrast study has fallen into disrepute, however, is that it is frequently poorly performed. The type of barium which is required for a dilute barium, high kilovolt technique, is totally inadequate for performing a barium-air contrast study. The dilute barium will adhere poorly to the mucosa on a barium-air contrast

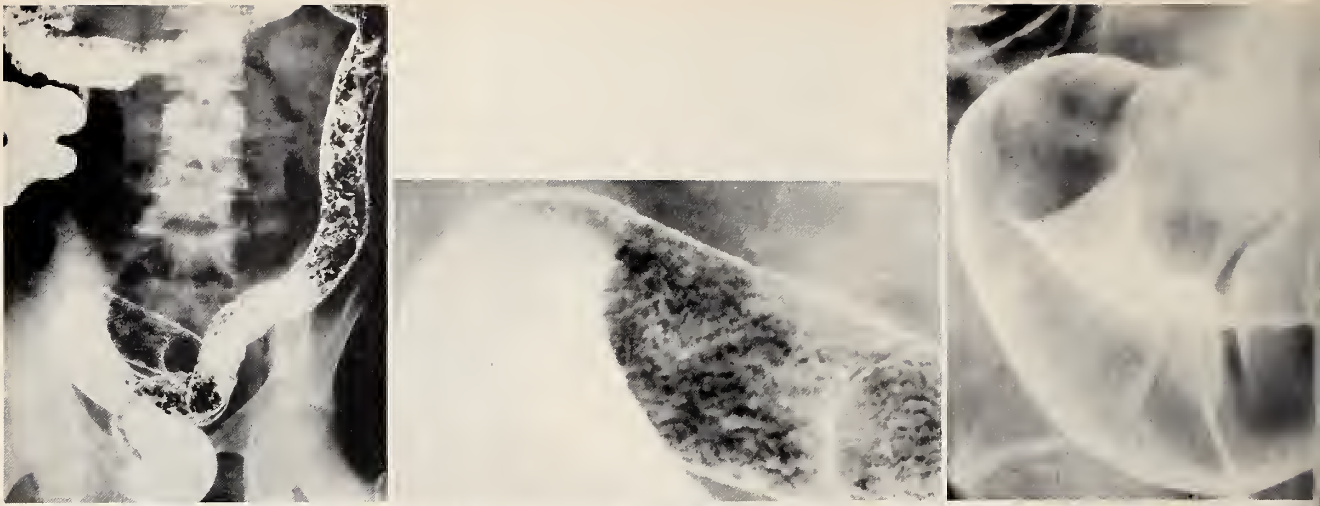

Figure 3.—Fourteen-year-old boy with ulcerative colitis. **Left,** the "jiffy enema" demonstrates **total colonic involvement.** Significant findings on tl radiograph include haustral abnormalities, a textured appearance of the mucosa of the sigmoid colon, and large pseudopolypi throughout the rest the colon, best seen in the descending colon. If one follows the outline of the medial border of the descending colon, one finds that it is relativ smooth and straight **despite the large intraluminal nodules.** This finding differs from the cobblestone pattern, which is seen in Crohn's disease and due to a combination of longitudinal and transverse fissures **protruding from the luminal outline.** The patient underwent colectomy a few days la because secondary thrombocytosis had resulted in venous thrombosis and multiple pulmonary emboli. The surgical specimen, fixed by distending it w formalin for 24 hours before opening it (Morson technique), confirmed the radiological findings. **Center,** magnified view of the sigmoid colon. Note h difficult it is to detect any abnormality of the outline of the barium-filled lumen on the reader's left. By contrast, one can readily recognize the textur appearance of the barium-coated mucosa seen face-on through the air-filled lumen on the reader's right. This textured appearance is due to mini ulcers which become visible on resected specimens only when inspected with a magnifying glass.[4] The author has never seen this appearance in patient with granulomatous colitis. **Right,** magnified view of the sigmoid colon (and cecal pole) in a normal subject, showing the difference between normal, smooth, featureless mucosa and the textured mucosa depicted in **center.**

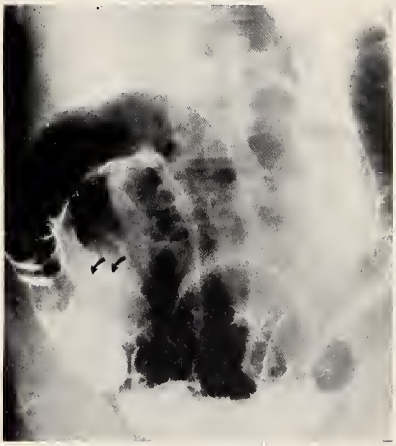

Figure 4.—"Jiffy enema" depicting haustral abnormalities and the textured mucosal pattern typical of ulcerative colitis. In addition, the terminal ileum is dilated (arrows) and has a similar finely textured appearance, typical of backwash ileitis. This appearance of the terminal ileum is extremely helpful in differentiating ulcerative from granulomatous colitis.

study and even in those areas where it sticks reasonably well it is too dilute to form a distinct shadow on the radiograph. For this reason, we never perform a barium-air contrast study on the same day as the dilute barium study. A barium-air contrast study requires a special dense, thick barium preparation which will form a sufficiently dense and thick coat on the mucosal surface to be clearly visualized throughout the colon.

At the St. Mark's Hospital in London, where a large number of patients who have colitis are examined radiologically, a special type of barium-air contrast study has been devised which is known as the "St. Mark's hospital instant enema."[4] At our institution, one of our student technicians renamed this the "jiffy enema" and this name has been used at Stanford for this procedure ever since.

The "jiffy enema" should only be used in a patient who has acute active colitis with diarrhea. The examination is possible because areas of active colitis contain no feces, whereas in the normal areas fecal material is abundant. This is particularly true of ulcerative colitis, which is characterized by constipation on the right side and diarrhea on the left. The examination presupposes that areas of active colitis are sufficiently auto-prepared for an air-contrast study. The patient is given no preparation and can have the examination immediately after being seen in the clinic or office.

A special barium preparation* is introduced into the colon until a large amount of fecal material is encountered. Barium is then drained from the rectum with the patient lying in the prone position and sufficient air is introduced to outline the colon. Fluoroscopy time should be kept to a minimum, preferably about 10 seconds, and only three 14 × 17 inch films need be exposed. These films are a postero-anterior prone view of the abdomen,

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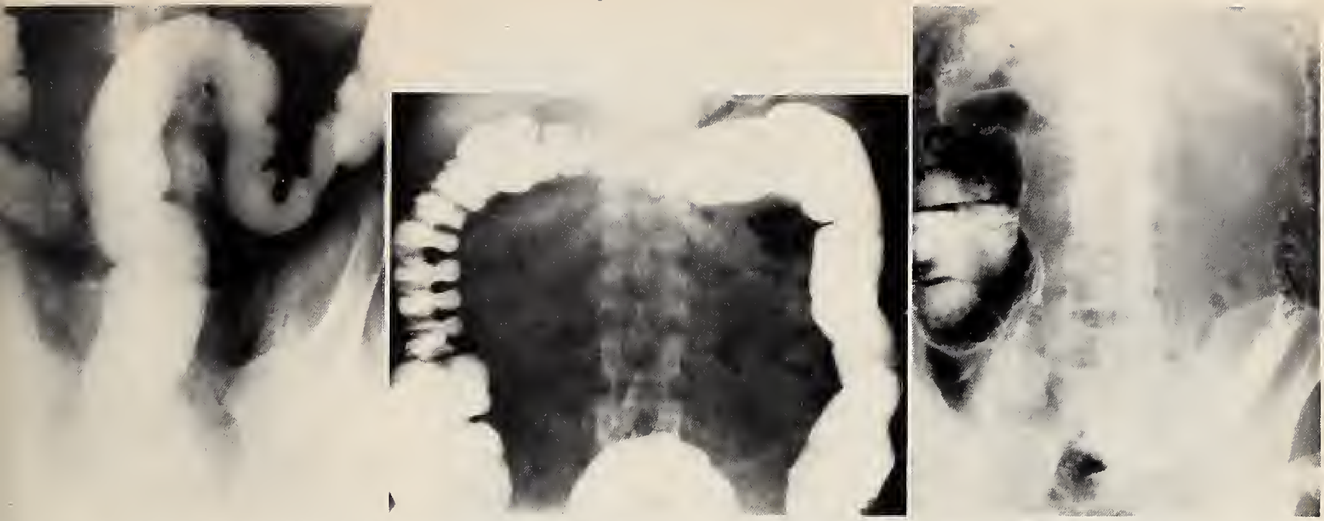
*Barium mixture devised by Roscoe E. Miller, MD, Professor of Radiology, Indiana University Medical Center, Indianapolis, Indiana: Barosperse, 1,000 ml, Mallinckrodt Pharmaceuticals, St. Louis, Mo.; 1,500 ml, Intropaque, Lafayette, Ind.; 2,500 ml water; specific gravity 6 using Philips Batest, Sweden; Viscosity 30-33 sec. using No. 4 Ford cup, Gardner Labs., Md.



gure 5.—Dilute barium enema high kilovolt examination technique, showing **left**, recto-sigmoid colon and **center** remainder of the colon. With the
ception of the cecum, the colonic lumen is narrowed, and the haustra of the transverse colon appear abnormal. This enema was misinterpreted as
rmal. **Right** barium-air "jiffy enema" one week later shows the abnormalities present with great clarity, and also reveals a finely textured rectum and
eudopolypi in the rest of the diseased colon.

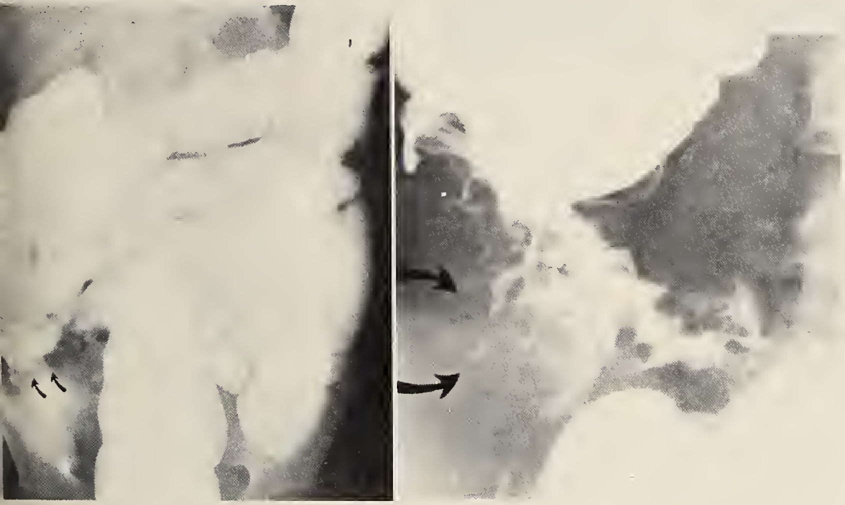


Figure 6.—Left, barium enema demonstrates irregular termination of the cecum with multiple fistulae (arrows). **Right**, spot films of the cecum and terminal ileum confirm the presence of fistulae (arrows). Barium has refluxed into the terminal ileum which appears grossly abnormal. Both the fistulae and the appearance of the terminal ileum strongly favor a diagnosis of Crohn's disease.

a lateral view of the rectum, and an upright film of the abdomen (Figure 2). The examination uses a minimum of films and a minimum of radiation. Since many patients who have ulcerative colitis or Crohn's disease of the colon are young, and require repeated examinations throughout their lives, the small radiation dosage which this method offers is an important consideration. An additional advantage of the method is that early, fine ulceration of the colon characteristic of ulcerative colitis can be clearly seen (Figures 2, 3, 4 and 5), whereas these features are invisible by the dilute barium, high kilovolt method. Not as much air need be introduced as in a conventional barium-air enema, only as much as the patient can tolerate comfortably. The discomfort the patient experiences with the air contrast enema is not a factor in this method. The method is contraindicated in any patient who is suspected of having a toxic megacolon, and should not be used in longstanding colitis where a carcinoma is suspected. In the latter case a conventional high kilovolt dilute-barium technique or a full barium-air contrast enema should be performed.

Roentgen Findings

Haustral changes. One of the characteristic features of any form of colitis, whether the colitis be ischemic, nonspecific ulcerative colitis, amebiasis, shigellosis, or radiation colitis, is that the colonic

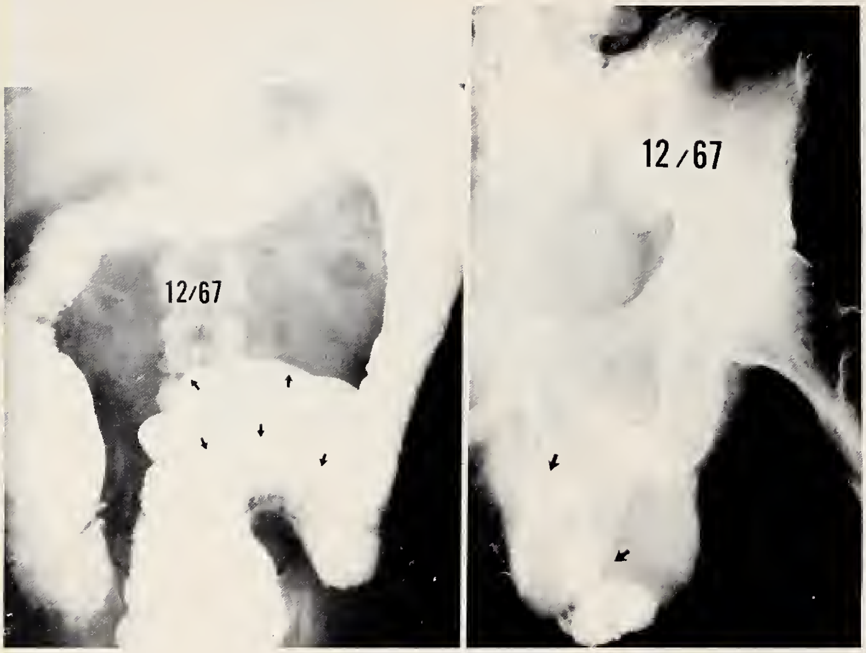


Figure 7.—**Left,** the barium enema shows haus abnormalities, excess intraluminal secretions, a large intramural abscess (arrows). **Right,** foll ing evacuation of the barium, a recto-scrotal fist has filled (arrows). Fistulae and intramural absces are characteristic of Crohn's disease.

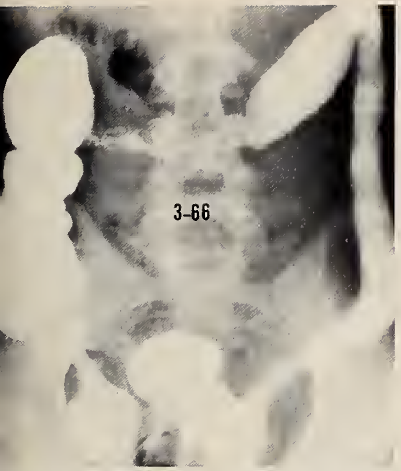
haustral pattern disappears. Additionally, any form of colitis can cause muscle spasm of the colonic wall and result in some shortening and narrowing. These features are completely nonspecific, and merely indicate that some form of colitis is present.

Significance of stage of the disease and previous therapy. Two studies have recently been published, one in the British[5] and one in the North American[3] literature, comparing the radiological features of ulcerative and granulomatous colitis. Both studies had certain serious deficiencies. In both, the patients had advanced disease, and the barium enemas studied were made before colectomy or autopsy. Presumably the radiographic appearance of the disease in both series had been modified by therapy, although neither group of investigators mentioned what therapy their patients had received. It has now been well documented that steroids, for example, can cause the radiological features of ulcerative colitis to disappear, particularly in the rectum.[2] This could account for the fact that in one series[3] the rectum looked normal in about one-fourth of the cases of ulcerative colitis. The stage at which the patient is seen is also of considerable significance with regard to the radiographic features which exist, as was previously indicated.

Early changes. During early disease, differentiation between the two conditions becomes difficult. The only feature which we have found to be consistently reliable in early disease is a fine, granular textured appearance of the involved area of the colon in ulcerative proctocolitis on a barium-air contrast study (Figures 2, 3, 4 and 5).

Important radiographic differences. In an experiment by Margulis et al[3] it was found that when radiologists looked at a combination of features present, 79 percent of them could accurately diagnose ulcerative colitis while 70 percent correctly diagnosed granulomatous colitis. Unfortunately, the report did not mention whether all the radiological signs which the investigators listed had to exist in order to make this differentiation, or whether they could make the distinction with, say, one sign, or three. For this reason, the conclusions are valueless as a guide to the practicing radiologist.

Certain features, however, can be extremely helpful in differentiating the two conditions. An attempt should always be made to see the terminal ileum by refluxing barium into this area. *If the terminal ileum is diseased, it appears distinctly different in the two conditions.*[3] Characteristically in Crohn's disease, the terminal ileum is narrowed and ulcerated, and has nodules; frequently small fistulae run between the terminal ileum and cecum (Figure 6). In the backwash ileitis of ulcerative colitis, however, the terminal ileum is widened and smooth or finely granular (Figure 4). The pres-



gure 8.—The cecum and the rest of the colon pear decidedly abnormal, whereas the ascend- g colon and hepatic flexure are not involved. ip areas suggest Crohn's disease, but can cur in ulcerative colitis.

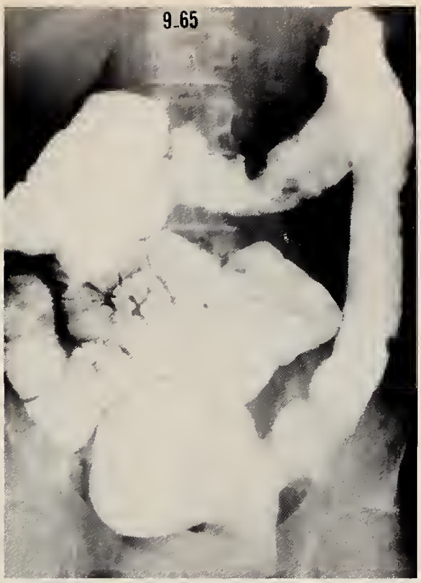


Figure 9.—The colon is abnormal from its mid-transverse portion distally. Haustra are absent in the left half of the transverse colon. Where the transverse colon overlaps the spine, haustra are absent on the inferior border, but are present (albeit abnormal) on the superior border. Absence of haustra along one wall, with retention of haustra on the opposite wall, favors a diagnosis of granulomatous colitis, but can occur in ulcerative colitis.

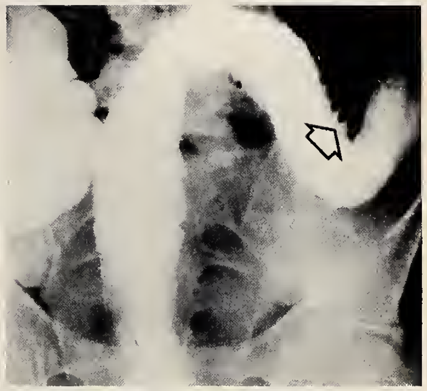


Figure 10.—Barium enema examination of the same patient shown in Figure 1. The rectum and sigmoid colon are narrow, thick-walled and irregular. Several rose thorn-like ulcers 6 mm in depth are visible in the sigmoid colon (arrow). The depth rather than the shape of these ulcers points to a diagnosis of Crohn's disease.

ence of fistulae and abscesses strongly suggests granulomatous rather than ulcerative colitis[3] (Figure 7).

As in the plain abdominal film, demonstration of the *thickness of the wall* can help differentiate ulcerative from granulomatous colitis. Ulcerative colitis is predominantly a *mucosal* lesion with little mural thickening. By contrast granulomatous colitis is a *transmural* disease and will frequently result in considerable mural thickening. The radiologist should, therefore, carefully measure the distance between the barium-filled lumen and the fat line running on the outer wall of the colon, which is particularly prominent in the patients who have granulomatous colitis.

The distribution of the disease often differs in the two conditions, although the value of recognizing this difference has probably been overstated in the past. Colitis on the right side strongly points to granulomatous colitis (Figure 6) while involvement of the left side in continuity with the right side suggests ulcerative colitis (Figures 2, 3, 4 and 5). Overlap occurs, however, particularly when the colitis affects the left side. "Skip areas" (areas of normal bowel between diseased bowel) tend to point to a diagnosis of granulomatous colitis (Figure 8), although this feature can occur in ulcerative colitis, particularly in the treated case.

The way in which colonic haustra are involved tends to differ in the two diseases. When colonic haustra disappear in ulcerative colitis, they tend to do so on both sides of the colon simultaneously (Figures 2, 3, 4 and 5). In granulomatous colitis, however, haustra tend to disappear along one wall of the colon while they are retained on the opposite wall (Figure 9). Even in this feature, some overlap tends to occur in the two conditions. In granulomatous colitis, thick transverse haustra are sometimes seen, an appearance which is infrequent in ulcerative colitis.

At one time, the shape of the ulcers that were present was thought to be rather characteristic of the two conditions.[4] Like pathologists, radiologists are prone to use nonscientific descriptive terms for the various features they see. Ulcers can resemble spikes. Such spikes are either straight or hooked. Hooked spikes resemble rose thorns, so radiologists have called this type of ulcer the "rose thorn-like" ulcer[4] (Figure 10). Thin straight spikes look rather like raspberry thorns, and have become known as "raspberry thorn-like" ulcers[4] (Figure 11). Some ulcers have a short tubular portion adjacent to the lumen, but then expand

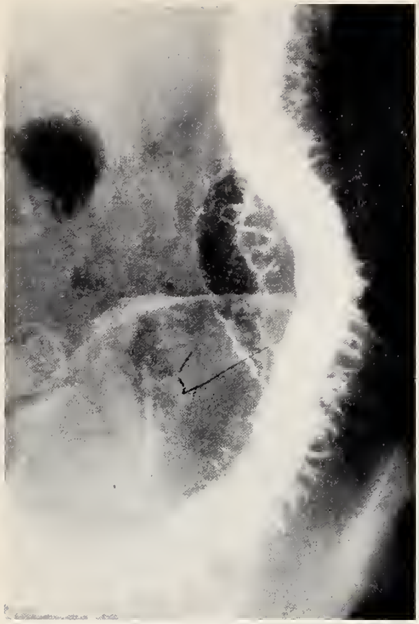


Figure 11.—Post-evacuation film following a barium enema showing multiple spike-like ulcers 8 to 9 mm deep. Ulcers of this depth are not seen in patients with ulcerative colitis. Their number and depth forecast that the patient will not benefit from a diverting (bypass) ileostomy.[1]

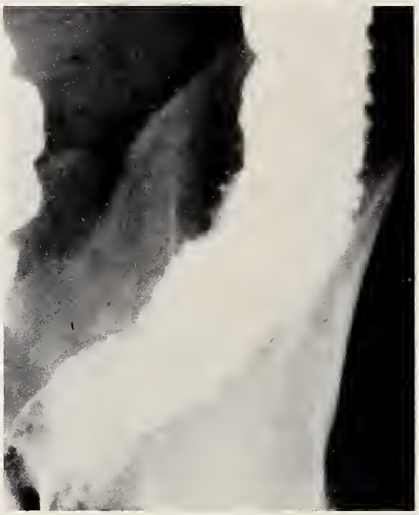


Figure 12.—Collar stud-like ulcers 3 to 4 mm deep in a patient with ulcerative colitis. Similar ulcers occur in patients with granulomatous colitis.

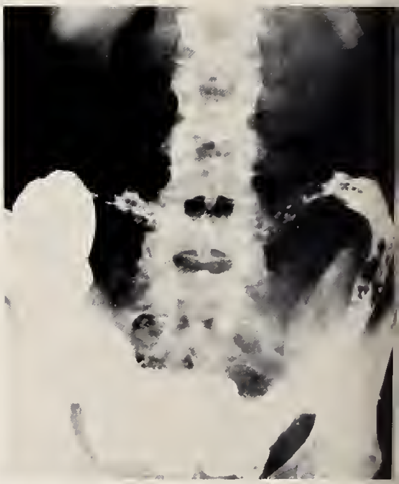


Figure 13.—Post-evacuation film after a bari enema. Note the cobblestone pattern of t left half of the transverse colon. The appearan of the colon distal to this is probably due pseudopolypi projecting into the lumen.

as they extend deeper into the wall, to resemble a collar stud, the so-called "collar stud-like" ulcer[4] (Figure 12). Others lack the short tubular neck and expand in the portion of the wall which lies immediately adjacent to the lumen, the so-called "sac-like" ulcers.[4] But, irrespective of whether the ulcers resemble a straight spike, a raspberry thorn, a rose thorn or cobblestone, recent studies have shown that the depth rather than the shape of the ulcer is important in differentiating the two conditions. Using a depth of 2 mm to distinguish superficial from deep ulcers, Margulis et al[3] could not find a sufficiently distinct difference between ulcerative colitis and granulomatous colitis. However, using a depth of 3 mm, Stanley et al[5] found a rather significant difference. The deeper the ulcer becomes, the more likely will the patient have granulomatous colitis. Margulis et al[3] said, "Deep fissures extending several millimeters perpendicular to the bowel lumen were seen exclusively in granulomatous colitis." Likewise, Stanley et al[5] stated:

"Although we took 3 mm as the minimum depth for ulcers to be classified as deep, many of the patients with Crohn's disease had ulcers up to 5 or 6 mm in depth. We found no correlation between any type of ulcer and one or other type of colitis. *Depth* was the differentiation factor. Deep ulcers, irrespective of type, would seem to be valuable evidence of Crohn's disease."

In Crohn's disease, we have recently found that the depth of ulcers present may be important in deciding whether a diverting ileostomy will succeed or not.[1] If the patient has numerous ulcers 5 mm or greater in depth, a diverting ileostomy will not succeed.[1] Pathologically, ulcers 5 mm or greater in depth destroy the muscularis propria of the colonic wall. These ulcers heal by fibrosis within the muscularis propria. The greater the destruction of the muscularis propria, therefore, the more likely will irreversible changes occur.

The cobblestone-like pattern (Figure 13), best seen on either the postevacuation films or on air-contrast studies, is characteristic of Crohn's disease. This should be differentiated from pseudopolyps, which can occur either in Crohn's disease or in ulcerative colitis. In pseudopolyps, the polypoidal lesions project into the lumen from an otherwise rather straight and regular luminal outline (Figure 3). Cobblestoning, however, is due to transverse and horizontal intersecting fissures, which project from the luminal contours as definite spikes (Figure 13). Sometimes the radiologist cannot decide which of the two is present.

Certain features such as toxic megacolon, presence or absence of a lesion suggesting cancer, and the presence of thumbprinting are so nonspecific as to be valueless in making the differential diagnosis.

Other diseases which cause similar changes. This paper primarily discusses the differential diagnosis between ulcerative colitis and Crohn's disease. It presumes that the clinician has excluded other lesions which can mimic the two conditions exactly. Amebiasis, tuberculosis, shigellosis, and schistosomiasis, for example, can resemble either disease. Radiation proctocolitis can also exactly simulate ulcerative colitis, but knowledge of the clinical history should exclude this possibility. Ischemic colitis can look exactly like ulcerative colitis during the active phase, and in the healing phase it can form large sacculations which resemble the eccentric involvement of granulomatous colitis. Scleroderma, dermatomyositis, amebiasis, and tuberculosis can also at times produce the haustral pattern seen in Crohn's disease.

When all the radiological features are considered together, the radiologist can usually distinguish granulomatous from ulcerative colitis. Some overlap does occur, but this will depend on the stage of disease, the radiographic techniques used, and the way in which therapy has modified the disease. The exact degree of overlap is rather difficult to ascertain because the best radiological studies reported to date[3,5] have not separated patients into the four categories which the radiologist encounters in practice: patients who have early disease, those with moderately-advanced disease, those with advanced disease and those with treatment-modified disease. Such categorization might enable the radiologist to differentiate the two diseases more accurately than is currently possible.

Summary

In patients who have active colitis, a modified barium-air contrast enema, called "the St. Mark's Hospital instant enema" or "the jiffy enema," produces diagnostic radiographs at low radiation dosage to the patient. Using this technique, the radiologist can recognize the typical fine, granular, textured appearance of the mucosa in ulcerative colitis. This corresponds to the friable, granular mucosa seen at proctoscopy. The terminal ileum, if diseased, is widened and smooth or granular when the backwash ileitis of ulcerative colitis is present.

By contrast, in Crohn's disease, the terminal ileum is narrowed, ulcerated and has nodules; frequently, small fistulae run between the terminal ileum and the cecum. Superficial colonic ulcers occur in both conditions, but the presence of deep ulcers (3 to 9 mm in depth) strongly favors a diagnosis of Crohn's colitis. Thickening of the colonic wall and the presence of fistulae and intramural abscesses are characteristic of Crohn's disease. Many other conditions simulate both ulcerative colitis and Crohn's disease radiologically, and have to be excluded on clinical grounds.

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PART II

Medical Treatment of Inflammatory Bowel Disease

GARY M. GRAY, MD, *Stanford*

IN THE DISTANT PAST regional enteritis and ulcerative colitis were considered as the only chronic diseases causing inflammation of the small intestine and the large intestine respectively. It was not until 1959 that it became widely appreciated that inflammatory bowel disease of the colon should be

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subdivided into ulcerative colitis and granulomatous colitis.[1,2] The use of new categories was necessary because there is a distinct inflammatory disease that appears to be much like regional enteritis and yet is usually confined to the colon.

Regional enteritis is often called Crohn's Disease or terminal ileitis[3] and most commonly involves a segment of lower ileum between 6 and 18 inches in length with a chronic inflammatory process that involves all layers of the bowel. It may also involve segments several inches long in other areas of small bowel including the duodenum or jejunum. The serosal surface of the bowel wall is covered with fat so that the appearance at operation is essentially characteristic for the disease. Typically there is involvement of the entire bowel wall with a chronic inflammatory process, often with the presence of non-caseating granulomata. Although originally believed to be a "surgical disease," it has been known for at least 20 years that a minimum of 50 percent of patients who have the lesion surgically resected will have recurrence that causes significant clinical symptoms within a period of two to five years after operation and frequently requiring additional operation. Because of this, it is now considered to be a disease to be treated conservatively, with resort to operation recommended when complications such as obstruction, bleeding or fistula formation occur. Symptoms caused by regional enteritis include cramping abdominal pain, anorexia, fatigue and diarrhea usually unassociated with malabsorption. Anemia due to ileal malabsorption of Vitamin B_{12} occurs in a minority of patients. Because of the frequent failure of surgical cure, long-term drug therapy is the treatment of choice unless complications of obstruction or bleeding occur.

Ulcerative colitis is an inflammatory disease involving the superficial layers of the colon mucosa. It is usually confined to the rectal and sigmoid colon, but in a minority of patients involves more proximal areas of colon in stocking-like fashion and may affect the entire colon. Classical symptoms are intermittent constipation and passage of blood early in the disease; in advanced stages there may be severe intermittent bloody diarrhea coupled with debilitating constitutional symptoms. Histologic features are completely different from those found in regional enteritis; involvement is usually limited to the superficial epithelial layers with the predominant histologic features of multiple micro-ulcerations and abscesses in the crypts. The principal serious complications of ulcerative colitis are sudden onset of severe constitutional symptoms and toxicity associated with a dilated colon, the so-called toxic megacolon[4] and, as a result of long-term active inflammatory disease, a high incidence of carcinoma of the colon. When ulcerative colitis has its onset in childhood, the risk of cancer is even higher, reaching 10 percent in those afflicted with colitis for ten years.[5] In adults, the risk of cancer increases with the duration, extent of involvement and the degree of clinical activity of the disease.[6] In severe toxic disease or where colon carcinoma is strongly suspected, total proctocolectomy is curative for this disease. However, for the vast majority of patients intermittent or continuous drug therapy is the treatment of choice.

TABLE 1.—*Features Differentiating Ulcerative and Granulomatous Colitis*

	*Ulcerative**	*Granulomatous**
Abdominal Pain	3+	4+
Diarrhea	4+	4+
Rectal Bleeding	4+	1+
Fistulas	1+	3+
Distal Disease	4+	1+
Proximal Disease	2+	3+
"Skip Areas"	0	3+
Histology		
Crypt abscesses	4+	2+
Penetrating ulcers	0	3+
Granulomata	1+	3+
Steroid Rx Effective	3-4+	2+

*0-4 represents relative degree.

Granulomatous colitis, often called Crohn's disease of the colon, has been identified in recent years although formerly it was included under the category of ulcerative colitis. However, it can be differentiated from ulcerative colitis on both clinical and histological grounds.[7] Table 1 shows the relative importance of clinical presentation, histological findings, and response to conventional therapy. Dr. Friedland in Part I has outlined the characteristic x-ray findings in each type of colitis.

Although granulomatous colitis does not appear to be associated with a pronounced increase in incidence of cancer of the colon, it is a relentless disease with a very stubborn and resistant course and is much more difficult to treat clinically than is ulcerative colitis. It usually comes to attention because of watery, non-bloody diarrhea associated with cramping abdominal pain and anorexia. Fistula formation, either recto-cutaneous or entero-

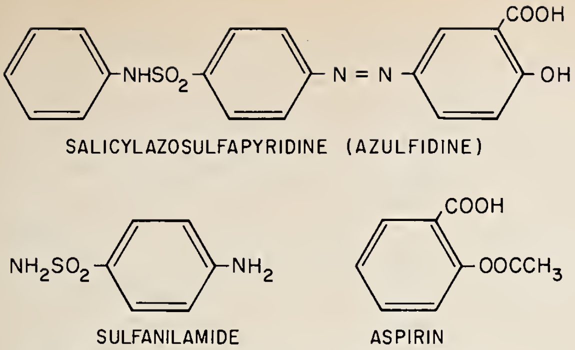

Figure 1.—Structure of salicylazopyridine.

enteric, is a frequent complication in the disease. Involvement occurs in skip-like fashion with intervening areas of normal colon between the diseased segments. Surgical resection of the disease segments is met with a high rate of cure, but there is definite recurrence in a minority of patients. Total colectomy is probably curative in a high proportion of patients but ileostomy complications do develop in some cases, requiring surgical revisions. For mild and moderate disease, drug therapy is the treatment of choice.

Treatment with Drugs

The most effective therapy for the vast majority (75 to 90 percent) of patients with one of the inflammatory bowel diseases is provided by drugs that depress the inflammation. Despite this, the most common reason for referral of a patient with inflammatory bowel disease to a major medical center is uncertainty about the use of anti-inflammatory agents.

Steroid enemas in ulcerative colitis. Mild ulcerative colitis of distal colon associated with intermittent bloody diarrhea as the sole symptom is the most common form of inflammatory bowel disease seen by practicing physicians. Corticosteroid enemas can be administered and have been shown in controlled studies to be very effective in producing healing of mucosal lesions. Since such patients have primarily rectosigmoid disease, enema preparations allow a high concentration of corticosteroid to come into direct contact with the diseased mucosa. When disease is quite active, two enemas a day can be given, one in the morning and one at bedtime. Hydrocortisone 100 mg or its equivalent is placed in 60 to 100 ml of saline solution. For mild disease, a single enema at bedtime with the patient lying on the left side is usually sufficient. It is critical that the patient retain the contents of the enema. Only water-soluble steroids such as Hydrocortisone hemisuccinate or Prednisolone 21 Phosphate have been shown to be effective in controlled trials.[8] Some physicians have advocated giving non-water-soluble steroids (for example, cortisone alcohol in safflower oil in enema form) to patients with seemingly high success rates. Since the efficacy of cortisone in oil has not been demonstrated in carefully controlled studies, it is probably not advisable to recommend administering steroid enemas in this way.

Salicylazosulfapyridine (Azulfidine®) is a drug that was demonstrated some years ago in carefully controlled studies to be effective in mild ulcerative colitis and to decrease the frequency of recurrent attacks in ulcerative colitis.[9,9a] This drug, as is shown in Figure 1, has a structure that includes the structures of both aspirin and the sulfas. The reason the drug is successful in preventing attacks of ulcerative colitis and probably also in aiding in mild colitic disease has not been demonstrated. However, it is certainly clear that when given in doses of 1.0 to 1.5 grams four times a day this drug is effective in ameliorating mild ulcerative colitis and in preventing serious recurrent attacks in people who are in remission. Though it has not been clearly demonstrated that the sulfas or aspirin are effective in ulcerative colitis, there is some suggestion that sulfasoxazole (Gantrisin®) is therapeutic. Azulfidine has side effects reminiscent of those of both aspirin and sulfas—nausea, various skin rashes and blood discrasias may occur. This drug has not been shown in controlled trials to be successful in the treatment of granulomatous colitis or regional enteritis. Even so, it is commonly believed that it is effective in these disorders and it has been widely used in clinical practice in the Western world. Overall, its use is recommended for mild ulcerative colitis at a time when the patient has minimal symptoms and in all patients with documented colitis who are in remission.

Treatment probably should be continued for a year or more in symptom-free patients before discontinuation is considered. The author has seen two patients with ulcerative proctitis become completely asymptomatic with reversion of rectal mucosal changes to normal in seven to fourteen days after Azulfidine therapy. However, after one year of successful Azulfidine prophylaxis, both patients had recurrent disease within 30 days after the drug was discontinued. Hence, it may be advisable to continue Azulfidine indefinitely if no serious side effects occur.

Oral corticosteroid treatment. For more serious manifestations of inflammatory bowel disease, prednisone given orally is the treatment of choice and there is suggestive evidence that distal colonic disease should be simultaneously treated with rectal steroids.[10] Ninety percent of patients with ulcerative colitis and at least 50 percent of patients with regional enteritis or granulomatous colitis respond initially to 40 to 60 mg of prednisone given daily in a single dose in the morning for two to four weeks. Rapid tapering of the prednisone is associated with a high incidence of recurrence of serious symptoms and hence dosages are usually decreased slowly (by reductions of 2.5 to 5 mg twice a week) to a level of 10 to 15 mg per day. Thereafter tapering is continued as long as no symptoms recur. Although the known side effects of cushingoid changes occur, more serious complications of upper gastrointestinal bleeding or psychosis are extremely unusual in inflammatory bowel disease for reasons that are not known.

Azathioprine (Imuran®). The use of azathioprine in ulcerative colitis and granulomatous colitis has recently been proposed because of the hope that immunosuppression could somehow ameliorate the manifestations of the disease. There have been a series of case reports which have appeared to show very encouraging results with this drug.[11,12] However, no controlled studies of this drug in inflammatory bowel disease have yet been accomplished and our use of this drug in several very ill patients with regional enteritis and granulomatous colitis has been somewhat disappointing. However, we have found it possible to reduce the maintenance dose of prednisone from 40 to 10 mg a day in several patients who previously had become severely ill whenever attempts were made to lower the steroid dosage.

The drug is usually given in doses of 100 mg a day and corticosteroid treatment is lowered as the immunosuppressive effect becomes manifest. It usually requires at least 30 days of therapy before any result can be detected. Ideally, a controlled trial should be undertaken in order to document the value of this drug in inflammatory bowel disease, especially since development of malignancy appears to be a complication of chronic azathioprine therapy.[13]

Drugs used solely for treatment of symptoms. Ancillary drugs to control the diarrheal aspects of the disease are diphenoxylate HCl-atropine sulfate (Lomotil®), in dosage of 1 to 2 tablets four times a day and deodorized tincture of opium (10 to 20 drops in water four times a day). Many patients with mild to moderately active inflammatory bowel disease can be kept in clinical remission by simple use of these diarrheal drugs which operate primarily by their local effect on the bowel to decrease motility. Although they are narcotics or narcotic analogs, serious complications including psychological dependence have occurred rarely during long-term use. Anticolinergics, such as propantheline bromide (Probanthine®) may also be utilized to control the rapid transit time that may occur in inflammatory bowel disease. Occasionally, use of these bowel-slowing drugs is associated with the abrupt onset of toxic megacolon, and all such drugs should be stopped immediately whenever this serious complication is suspected.

If the physician uses the drugs discussed above in a judicious manner, the majority of patients with inflammatory bowel disease can be maintained in reasonably good health. Surgical operation should be reserved for acute complications (such as stricture, bleeding, suspected cancer) and for chronic disease with constitutional symptoms that are refractory to steroid therapy.

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PART III

Operative Therapy for Ulcerative Colitis and Crohn's Disease

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IT IS NOW GENERALLY ACCEPTED that ulcerative colitis is a disease primarily and solely of the large intestine whereas Crohn's disease may affect the alimentary tract from the esophagus to the rectum. Crohn's disease of the colon (granulomatous colitis) is common either in association with small bowel disease or affecting the large bowel alone. In our experience the extent of small bowel involvement is more limited in extent than that found in regional enteritis without colonic involvement. The pathogenesis, clinical features and radiological findings of these two disease entities have already been discussed. The implications of surgical operation for these two diseases is simple for ulcerative colitis but complex in the case of Crohn's disease. Since ulcerative colitis is confined to the colon, it can be eliminated when indicated by eradication of the large intestine. Not so for Crohn's disease, since it can affect any portion of the alimentary tract and recurrence is commonplace after resection. However, it is of interest that the surgical management of Crohn's disease of the colon fares better than the surgical treatment of regional enteritis. This will become evident as we go into more detail regarding the surgical management of Crohn's disease.

Indications for Operation

The indications for operative intervention for these two diseases are similar in some respects. When either disease becomes refractory to medical therapy that has included salicylazosulfapyridine (Azulfidine®), systemic or local use of corticosteroids or immunosuppressive therapy, operative intervention is indicated. Similarly, significant retardation of growth and maturation in adolescence either due to the disease process or to the drug therapy is a most important criterion for surgical treatment. Likewise, complications from prolonged administration of corticosteroids or immunosuppressive agents in adults should direct these patients to the surgeon.

When we examine the complications of the two disease processes, we find differences that have important implications with regard to surgical management. In ulcerative colitis we may encounter uncontrollable hemorrhage, toxic megacolon, perforation, progressive liver disease, and the risk of carcinoma with long standing disease—all indications for operation. On the other hand, bowel obstruction and internal fistulization are uncommon. The complications of Crohn's disease that require operation include intestinal obstruction due to cicatricial stenosis, and enterovesical, entero-vaginal and entero-cutaneous fistulae. Fistulae between loops of small bowel or small bowel and colon do not usually indicate surgical intervention. Massive bleeding is uncommon, as is free perforation and the development of carcinoma.

In addition to the specific indications discussed above, I hasten to add that it is important to assess the patient as a whole individual, not merely to examine his disease process. It is important to know whether he (or she) is capable of carrying on his normal work and activities, can enjoy a reasonably palatable diet, is not spending his savings on expensive medications for long periods of time, and is able to enjoy life in our customary fashion.

Preoperative Preparation for Elective Resection of the Colon

In addition to the routine history, physical examination and laboratory studies, all patients should have an electrocardiogram, chest film and liver function tests including determination of prothrombin time. Serum albumin deficits should be corrected with daily intravenous human albumin, and prothrombin deficiencies with vitamin K. Anemia, if present, requires correction with whole blood or packed cells before operation is done.

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Cystoscopy may be required in cases of bladder involvement by fistula. Since many patients are receiving or have been receiving corticosteroids, adequate steroid therapy must be given before, during and following operation.

The local preparation of the colon is an important aspect of preoperative management since it is highly desirable to have a clean, empty colon as free of pathogenic organisms as possible. Most surgeons are in agreement that mechanical preparation is as important or more important than the sterilization by antibiotics. The accomplishment of mechanical cleansing requires the use of a clear liquid diet for three to four days before operation. More recently, the use of elemental amino acid diets has been greeted with enthusiasm in bowel preparation. Adequate purging of the bowel with suitable laxatives is essential, as are cleansing enemas. I favor the use of neomycin or kanamycin for 48 to 72 hours before operation to reduce the bacterial flora of the colon. It should be remembered that most anaerobic organisms are still present in significant numbers after such antibiotic preparation.

Before operation a Foley catheter is inserted routinely to monitor the urinary output and to protect the bladder during the surgical procedure. A nasogastric tube is also inserted to decompress the stomach during operation and after operation.

Preoperative Preparation for Emergency Resection of the Colon

Partial or total colectomy in emergency may be necessitated by acute obstruction, massive hemorrhage, or by perforation or the development of toxic megacolon unresponsive to conservative therapy. Under these conditions it becomes impossible to carry out a careful preparation of the colon. It is imperative to correct any volume deficits with blood or albumin or both and to initiate vigorous antibiotic therapy. Central venous pressure monitoring is essential in these critically ill patients.

Operative Management of Ulcerative Colitis

Since removal of the entire colon is curative for ulcerative colitis, total procto-colectomy is the procedure of choice. A minimal length of ileum is removed, with the proximal end brought out through a pre-determined site in the right lower quadrant as a permanent ileostomy. The ileum is everted on itself and the edge sutured to the skin so that it projects between 1 and 2 cm above the skin level. It is important to suture the ileal mesentery to the lateral parietal peritoneum to prevent internal herniation or prolapse.

More recently, there is increasing interest in Kock's[1] operation in which a large pouch is made of the distal ileum. The pouch hangs in the pelvis and exits by a very small ileostomy. This pouch is capable of holding 12 to 24 hours' accumulation of ileal contents and is catheterized every 12 to 24 hours. Removal of the rectum is accomplished either via a combined abdomino-perineal approach or through the abdominal incision alone if the pelvic inlet is adequate. In males it is essential that dissection stay as close to the rectum as possible to avoid impotence. Surgical mortality ranges from 3 to 5 percent for elective operations.

Although some surgeons advocate ileorectal anastomosis when the rectum appears uninvolved with disease, the results in this country with this procedure have not been satisfactory.[2] It is my opinion that in many such cases the diagnosis is incorrect and that the patients have Crohn's disease rather than ulcerative colitis. The high incidence of recurrent disease, the risk of the development of carcinoma, and the tendency to frequency of bowel movements argue against this procedure except in rare cases.

More recently, sphincter-saving procedures have been devised and utilized successfully. Preservation of the distal anorectal segment from which the mucosa has been removed serves as a muscular tube which the distal ileum is pulled through and anastomosed to the cutaneous cuff of the anorectal line.[3] Further experience with procedures such as this is needed to evaluate the long term results.

Since one occasionally notes sparing of the right colon at the time of operation, it is tempting to preserve the right colon and to perform an end colostomy, thus avoiding ileostomy. In our experience the preserved right colon almost always becomes involved with disease, requiring right colectomy and ileostomy later. The pronounced reduction in ileostomy complications that has been brought about by the improvement in the technical aspects of constructing permanent ileostomies and the advances in ileostomy care contraindicate preserving the proximal colon in this disease.

When emergency operation is required for complications as severe hemorrhage, perforation or toxic megacolon, operative procedures less than total procto-colectomy may be indicated. It may be prudent to leave the rectum for subsequent removal rather than to prolong the operation unduly. Occasionally, diverting ileostomy has proved lifesaving in patients with toxic megacolon in whom a more extensive operation would not be tolerated. Turnbull[4] has advocated definitive ileostomy and transverse colostomy to decompress the dilated colon when walled-off colonic perforations are discovered at laparotomy. Selection of the appropriate procedure may reduce a recognized mortality of 30 to 40 percent to acceptable levels.

Operative Management of Crohn's Disease

Regional enteritis. In contrast to chronic ulcerative colitis that is cured by surgical eradication, Crohn's disease is characterized by its tendency to recur in a significant number of patients after operative therapy. Despite a recurrence rate of roughly 50 percent after operation for regional enteritis, we must not fail to recognize that an equal percentage of patients are cured by operative intervention. Furthermore, when the disease affects the colon primarily, the results are significantly better than for operations for small bowel disease.

Regional enteritis may present acutely as acute appendicitis; and when the patients are found to have a diseased ileum, resection is usually not necessary, since acute ileitis generally denotes the disease is in early phase. The appendix can be removed safely, provided the cecum is not also involved by the inflammatory process. In the latter circumstance, the risk of fistula formation is great if the appendix is removed. It is also important when terminal ileitis is present to culture material from the appendix for the presence of Yersinia enterocolitica or Yersinia pseudotuberculosis and to do the appropriate serological test. It is usually not possible to differentiate between these two forms of terminal ileitis. It is also of interest that signs of Crohn's disease have not developed in patients with Yersinia infection who were followed for periods up to five years.[5]

The surgical management of those complications of regional enteritis discussed earlier has usually consisted of resection or by-pass by exclusion. Simple by-pass by ileo-colostomy (side-to-side) has been abandoned since it does not result in complete diversion of the fecal stream and may result in the formation of a blind loop. Most surgeons favor resection as the procedure of choice when it can be safely carried out. The limits of resection tend to vary according to the preferences of the surgeon. It has been shown that radical excisions that remove more than 6 inches of normal-appearing ileum proximal to the grossly involved bowel have not lowered the recurrence rates as compared with more conservative resections. In addition, it has often been customary to remove the ascending colon, when uninvolved, in order to accomplish an ileo-colostomy anastomosis easily. I believe it is unnecessary to resect more than 6 inches of grossly normal-appearing ileum and the entire right colon. An ileo-cecostomy or end-to-end ileo-ascending colostomy are preferred, since it may be important to preserve as much of the right colon as possible to avoid postoperative diarrhea. If fistulae exist between loops of bowel, enterovesical or enterocutaneous, resection of the involved segment of bowel along with the fistulous tract is indicated. When the bladder is involved, the wall should be repaired with sutures placed through healthy tissue, and an indwelling catheter inserted for drainage.

Exclusion by-pass procedures are reserved for the occasional cases in which there is tremendous thickening and shortening of the mesentery, making resection dangerous. We have recently modified the operation where there has been extensive disease involving the entire ileum with or without skip lesions more proximal, particularly in adolescent patients. The segment of intestine bypassed has its proximal end closed and its distal end at the ileo-cecal junction transected and brought out the right lower quadrant as a mucous fistula. This modification insures a complete bypass. That is, it prevents any reflux of colonic materials into the diseased ileal segment. The rationale for this procedure is based on the striking remission that follows diversion by ileostomy for Crohn's disease of the colon.

When "skip areas" of disease are present, they may be resected along with the terminal ileitis if in reasonable proximity, but when they occur in the jejunum it is usually wise to leave them and resect only the severely diseased portion of the ileum. A conservative approach is usually justified, since one wishes to avoid the development of

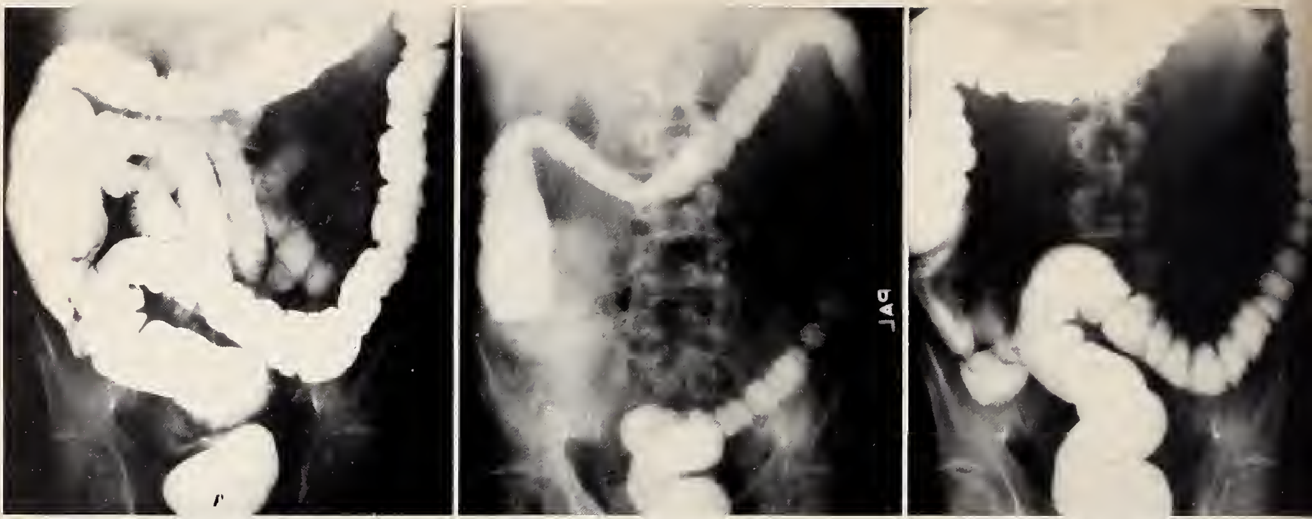

Figure 1.—**Left,** discontinuous and asymmetrical irregularity of the contour of the colon, most prominent in the proximal transverse and descending colo **Center,** evidence of healing with absence of ulceration two years following diversion. **Right,** colon normal four years after ileoileal reconstruction.

a short bowel syndrome, with diarrhea and inadequate absorption.

When Crohn's disease involves the duodenum, it may be necessary to perform a gastrojejunostomy for duodenal obstruction. We have seen Crohn's disease of the duodenum in association with duodenal ulcer disease and have achieved excellent results with vagotomy and pyloroplasty. Gastric involvement may require resection if the distal stomach becomes obstructed by granulomatous disease.

Crohn's disease of the colon. Crohn's disease of the colon may be diffuse in its involvement, or it may be segmental or, rarely, limited to the rectum. In addition, any of the forms above may be associated with involvement of the terminal ileum. In my experience, roughly 40 percent of patients with Crohn's of the colon also have ileal disease. It is of some interest that, in contrast to regional enteritis without colonic disease, ileal involvement has often been of limited extent.

Where the disease appears segmental, often with stricture formation, local excision with end-to-end anastomosis will yield satisfactory results in only 50 percent of patients, the disease recurring later in the other 50 percent. However, the results appear better in patients with right sided disease and with a normal left colon and rectum. Many surgeons will elect colectomy with ileo-transverse colostomy as the procedure of choice in these patients. The accepted therapy for diffuse disease of the colon is total procto-colectomy, with ileostomy proximal to ileal disease if present. Recurrent disease at the stoma, with retrograde extension, occurs in about 15 to 25 percent of patients. Since the rectum may be spared in Crohn's disease, it is often tempting when colectomy is indicated to do an ileo-rectal anastomosis, avoiding ileostomy. However, the long term results indicate a roughly 50 percent rate of recurrent disease—similar to the results of segmental colonic resections and those done for regional enteritis.

Despite the excellent results of total procto-colectomy for diffuse Crohn's disease of the colon, for the past decade we have been interested in the effects of diverting ileostomy. Our reports in 1968 and 1971[6] emphasized the immediate and dramatic clinical response seen in all patients following diversion. Objective improvement in the radiological appearance of the colon toward normal was also observed (Figure 1). It seemed most reasonable to recommend this approach in young patients rather than to remove the entire colon. Fifty percent of our reported cases were in patients under the age of 20, most of whom had the nutritional complications of the disease or its treatment with corticosteroids. Although we achieved excellent response in all 24 patients initially, eight (33 percent) of the group had recurrence of symptoms anywhere from six months to three years after the diversion operation and total procto-colectomy was necessary (Table 1). Nine patients (38 percent) remain asymptomatic for periods of from one to six years—unwilling to risk re-connection. The remaining seven patients (29 percent) have had intestinal continuity re-established (Table 2). Three patients of the group remain well (up to eight years after operation).

TABLE 1.—*Results of Ileostomy Diversion (24 Patients)*

- 24 Excellent initial response
  - 16 Continued remission (12 to 72 months)
    - 7 Re-united (24 to 36 months after by-pass)
    - 9 Remain asymptomatic (12 to 72 months)
  - 8 Relapse (6 to 36 months)
    - 8 Proto-colectomy (10 to 40 months)

TABLE 2.—*Results of Restoring Continuity (7 Patients)*

- 7 Re-united (24 to 36 months after by-pass)
  - 3 Asymptomatic (6 months, 60 months, 96 months)
  - 4 Recurrence (4 to 36 months)
    - 2 Procto-colectomy
    - 1 Re-by-passed
    - 1 Remission on medical therapy

Four have relapsed with two undergoing total procto-colectomy, one patient has had re-diversion by ileostomy with remission of symptoms, and one patient is in remission on medical therapy. Although we have restored the colon successfully in only three of 24 patients to date, we remain enthusiastic about the initial response to diversion and have avoided permanent ileostomy in enough patients to justify further clinical trials of this form of therapy.

Sequelae of Operative Therapy

Aside from recurrent disease after operation, which we have already discussed, there are other problems or sequelae that may develop following operative therapy. These include both local and systemic problems.

Local problems

Ileostomy revisions may be required in patients undergoing total procto-colectomy. The problems encountered include ileostomy dysfunction due to prolapse, stenosis or herniation of a loop of adjacent ileum about the ileostomy. Recent technical improvements in the construction of ileostomy stomas has considerably reduced these problems. Local skin problems are unusual provided the patient receives expert exterostoma care.

Failure of the posterior wounds to heal after proctectomy has plagued most surgeons. This problem tends to occur more frequently in Crohn's disease. There is no universal agreement as to why these wounds fail to heal, although various technical errors have been postulated. Therapy for this complication has included the use of local antibiotics and silver nitrate application, re-excision of the sinus tract, removal of the coccyx, and the application of skin grafts. The prevention of these problems has been approached by primary closure of the perineal wound over suction catheters with some success and the endoanal approach that removes the sphincter but spares the levators with their fascia.

Systemic problems

Since many patients operated upon for ulcerative colitis and Crohn's disease have been receiving corticosteroid therapy for long periods, difficulty in discontinuing steroids is not uncommon. In such cases a gradual tapering of medication over a protracted period as well as the use of ACTH is sometimes necessary. Too rapid withdrawal is often followed by symptoms and signs of adrenal insufficiency—weakness, nausea, vomiting, fever, and postural hypertension.

Since vitamin B_{12} is absorbed in the distal ileum, when the terminal ileum is removed in Crohn's disease the patient should receive monthly vitamin B_{12} therapy to prevent macrocytic anemia.

Extensive small bowel resection may result in the "short bowel syndrome." Diarrhea or excessive ileostomy outputs leads to malabsorption and electrolyte losses. The use of Lomotil® or tincture of deodorized opium often slows intestinal transit. The diet should be augmented with vitamins and calcium and magnesium, if necessary. Excessive losses in these patients over long periods may lead to demineralization of the skeleton, formation of urinary calculi, anemia, and varying degrees of malnutrition.

Summary

The operation of choice in chronic *ulcerative colitis* is total procto-colectomy with permanent ileostomy. In selected patients total colectomy with ileorectal anastomosis may be indicated.

In patients with *regional enteritis* resection of the involved segment is preferred over by-pass by exclusion. "Skip lesions" proximal to the severely diseased segment may be left intact unless obstructing.

Diffuse Crohn's disease of the colon is best treated by total procto-colectomy with permanent ileostomy. Consideration should be given to diversion by ileostomy alone, particularly in young patients.

Segmental Crohn's disease of the right colon may be treated successfully by local resection and ileo-transverse colostomy, whereas segmental disease of the transverse of left colon is best managed by total procto-colectomy.

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PART IV

The Ileostomy

Consideration of the Stoma, Peristomal Skin, Appliances and Diet

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IF MEDICAL MANAGEMENT of ulcerative colitis or regional enteritis has not been successful, surgical operation resulting in ileostomy may be necessary. Since toileting has been a personal, private matter since early childhood, the possible loss of control over this vital function is often overwhelming to the patient and his family. It is most important to provide the patient with a manageable ileostomy and teach him how to care for it. Stoma site selection, types of ileostomy, kinds of appliances, stoma and skin care, treatment of skin problems, and diet are important in the successful rehabilitation of the patient.

Once colectomy or by-pass ileostomy has been decided upon, choosing the stoma site is a consideration in the quality of the patient's life afterward. Various authors have described positioning of the stoma on the abdomen.[1,2] Certain criteria must be established before a decision can be made.

Since excrement may be liquid or soft and unformed and is eliminated day and night, an appliance must be worn 24 hours a day. It is therefore essential to place the stoma in an area manageable by the patient. He is the one who must care for it—often for life.

The site must be well away from all bony prominences—the costal margin, the superior anterior crest of the ilium and the symphysis pubis; and it must be such that the stoma will be visible to the patient when he is sitting or standing. Also it should be so chosen that articulation between the femur and the innominate bone will not interfere with wearing an appliance. Unusual contours, scarred areas and the umbilicus must be avoided. Although not usual in patients with ulcerative colitis or regional enteritis, obesity entails the additional restriction that the waist and abdominal folds also have to be avoided. Measurement for the stoma site should be made with the patient lying on his back, sitting up and standing, for a scar that is smooth with the patient supine may retract and pucker when he is sitting or standing. When the stoma site is not decided upon until the patient is in the operating room, this measurement in various positions is not done. Fortunately the iliac crest is most medial when the patient is supine, so the ileostomy usually is placed away from this most troublesome area. A well-healed pre-existing abdominal scar or the umbilicus causes far fewer problems than an ileostomy near the iliac crest.

Using these criteria, the stoma site usually is marked on the right side of the abdomen, below the waist, away from the iliac crest, the costal margin and the symphysis pubis and, in adults, at least two and a half inches from the umbilicus (see illustration). The ileostomy may be placed on the left side of the abdomen if the criteria can be better met there.

Stomas may be surgically matured or left nonmatured. The matured ileostomy is one that is constructed by bringing the ileum through the stoma site on the abdomen, trimming away the

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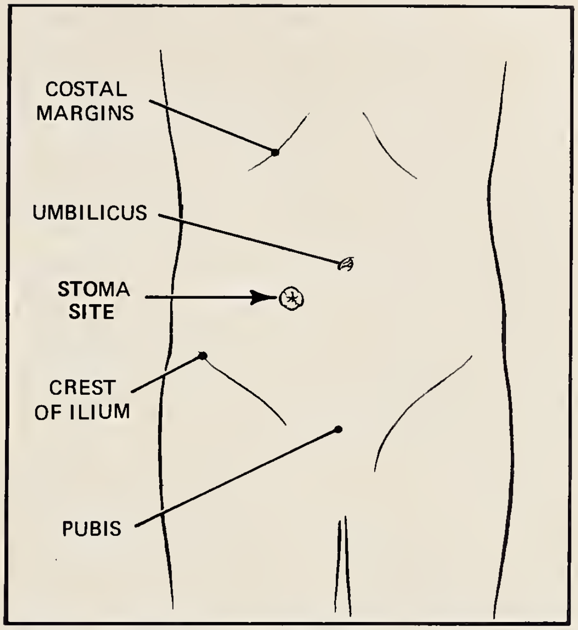
mesentery along the length to be left above the skin, and then cuffing the ileum on itself and suturing it to the skin. With the mesentery trimmed, the stoma opening can be centered, avoiding future problems with leakage of stool that might occur if the opening were pulled to one side. Tension on the abdominal tissues should be avoided lest horizontal folding in the peristomal skin leave creases along which fecal material could leak beneath the face-plate of the appliance. The matured stoma heals faster and more regularly, is less friable and is much easier to maintain hygienically. The non-matured stoma is constructed by bringing the ileum through the abdominal wall, suturing the serosal surface to the skin and clamping the distal end. The clamp is removed one to two days after operation and the stoma is allowed to heal, cuffing over on itself as it heals. This process takes four to six weeks and often results in an irregular mushroom-shaped stoma. It heals slower and stool often accumulates beneath it, causing skin breakdown. Such stomas are also known to constrict at the skin level as they heal. Moreover, they make it difficult to fit the patient with an appliance, and even though custom made appliances are available, it is better to construct the stoma so that the patient can use readily available standard equipment.

Stomas can protrude above skin level, be flush with the skin or be retracted below skin level. Stomas constructed or retracted below skin level cause the patient nothing but problems. Enzyme-rich fecal material puddles on the skin and causes erythema and excoriation. In most cases surgical revision is necessary sooner or later. The skin level ileostomy causes the same problems to a lesser degree but still is troublesome.

With a matured stoma constructed so that it protrudes above skin level at least 1 cm and no more than 2 cm, the patient can carry out ileostomy toilet with a minimum of trouble. The stool falls into the appliance pouch and the skin is protected from irritation. There are usually no trauma problems with a stoma of this type, but one that protrudes more than 2 cm may cause a patient some concern if interpreted as a phallic symbol. This is distressing to young girls particularly, but also to women and men; and adjusting to an ileostomy is difficult enough without this additional anxiety. If a patient gains or loses more than 10 pounds in weight the stoma may change size and shape or become retracted or more elevated above skin level.



Stoma site should be below the waist and well away from all bony prominences.

Appliances

Since an appliance must be worn continuously to collect stool, choosing one is of prime importance. There are many companies throughout the United States that manufacture good ileostomy equipment and most patients get along well with it if the ileostomy is properly constructed and placed. Literature and product samples are readily available from manufacturers. Following is a list—not complete—of suppliers of ileostomy equipment. No one manufacturer is recommended over another.

Atlantic Surgical Co., Inc., 1834 Lansdowne, Merrick, New York 11566
Davol, Inc., Providence, Rhode Island 02901
John F. Greer Co., 5335 College Avenue, Oakland, California 94618
Gricks, Inc., Hollis, New York 11423
Hollister, Inc., 211 East Chicago Avenue, Chicago, Illinois 60611
Marlen Manufacturing and Development Co., 5150 Richmond Road, Bedford, Ohio 44146
Marson Manufacturing Co., Wausau, Wisconsin 54401
Nu-Hope Laboratories, 2900 Rowena Avenue, Los Angeles, California 90039
Permatype Co., P.O. Box 175, Farmington, Connecticut 06032
Torbot Company, 1185 Jefferson Boulevard, Warwick, Rhode Island 02886
United Surgical Supplies Co., 11775 Starkey Road, Largo, Florida 33540

Appliances may be made in one piece or may be composed of several parts that must be assembled. All commercial appliances have features in common. They consist of a face-plate (or mounting ring) that is made to adhere to the peristomal skin with glue or other adhesive material, a collecting pouch for the stool, and a bottom opening from which to empty stool.

"Choosing an appliance," a man from Montreal is reported to have said,[3] "can be like choosing a wife: it should be well-shaped, neat in appearance and light weight, smell nice, easy to get along with, dependable, close to you at all times, and stick to you in moments of stress."

This is indeed true, and considerations regarding choice of appliances are basic. The opening in the face-plate must be carefully measured and be only one-sixteenth inch larger than the stoma. The snug fit prevents escape of fecal material that would irritate peristomal skin. Most equipment is made for circular stomas. If an irregularly shaped stoma permits stool to leak onto the peristomal skin, a custom-made opening in the face-plate may be necessary. Most manufacturers will construct whatever opening is needed. A face-plate with an outer diameter of 3½ inches is adequate for most adult patients, even though most companies refer to this dimension as "child size."

Face-plates may be made of natural rubber, synthetic rubber, vinyl plastic or rigid plastic, and they may range from very flexible to firm. Ideally they should not absorb odors, but natural rubber unfortunately does become malodorous with use. Some synthetic rubbers are better in this regard, though in time they too absorb odor. With the rigid plastic face-plates this difficulty is overcome, but they do not conform to the body as well as the more flexible materials.

Convexity of the face-plate is determined individually. For most patients a slightly convex plate is best. Generally, the firmer and flatter the abdomen, the less convexity needed. The softer the abdomen or the more retracted the stoma, the more convex the face-plate should be. An obvious contradiction to this is the pregnant woman or the small, lean child. In such cases the abdomen is firm and convex and a flat, flexible face-plate is needed to mold to the contours. An example of the opposite extreme is the overweight person with much soft adipose tissue over the abdomen and a stoma that is flush with the skin or retracted stoma. He would require a fairly deep convex face-plate that will sink into the abdominal tissues and mold to the contours to prevent leaking of stool.

The face-plate must be attached to a pouch to collect the stool. Pouches are made of rubber, vinyl plastic or soft thin plastics such as polyethylene. Most rubber pouches become odorous with continuous use. So do vinyl pouches, but they are less expensive and can be discarded after several weeks. Each has its advantages. Rubber pouches are heavier and bulkier but last six months or longer. Vinyl pouches are lighter but are more likely to leak at the seams. If a patient has short bowel syndrome, vinyl pouches cannot be used because usually in a week or so they become brittle. Synthetic rubbers such as butyl pouches are effective in short bowel syndrome because they stay soft and give protection from odor. The opening through which the stool is emptied must be large enough for quick emptying and easy to clean. The opening may be secured with plastic clamps, clips or rubber bands. A cloth cover for the pouches is suggested to protect the skin.

Pouches are available in transparent, translucent and opaque materials. Some patients use closed-end, thin, transparent bags which they detach from the face-plate and dispose of every three to five hours. Others who have tried this method find that removing the bag disturbs the seating of the face-plate and leaks occur earlier.

Use of glues to secure the face-plate to the abdominal skin has become less popular since the advent of double-faced adhesive discs, which are easier to apply and need no time to dry. With them, the time needed to change the appliance is greatly lessened. The only advantage of glues now is that they may hold the face-plate in place a day or so longer than the discs. Ninety percent of patients are able to wear an appliance using double-faced adhesives for four or five days between changes. Even newer are the gelatinous cellulose or synthetic polymer wafers which create a most effective nonirritating seal.

Before the face-plate is pressed into place, a sealant material must be placed around the stoma so that the enzyme-rich stool will not come into contact with the skin. The best substance for this purpose is karaya, a water-soluble gum from the Sterculia urens bush in India. It is available in solid or powder form. Washers made of this substance, with center openings the right size to fit snugly around the stoma, give adequate protection against leakage. Karaya has a healing effect on irritated skin and for this reason larger washers the same size and shape as the face-plate, with a small hole in the center to fit around the stoma, are sometimes used instead of the adhesive discs.

Almost all ileostomy face-plates are equipped with loops, so that they may be suspended from a belt worn around the waist. Usually, however, the face-plate is secure enough and this suspension is not needed unless there are problems with leakage or the patient contemplates vigorous exercise that might dislodge the plate. Because of the discomfort and the possibility of erythema or even ulceration at pressure points, patients should first try to get along without a belt, using one only in the circumstances mentioned above.

If a belt must be worn, care must be taken to position it and adjust the tension so that it does not creep upward, pulling upon the face-plate and putting traumatic tension on the stoma as the patient walks or stretches. If fasteners or folds in loops press uncomfortably against the skin, pads should be placed at the pressure points.

Changing the Appliance

A typical procedure for changing an appliance involves assembling all necessary equipment and supplies—the appliance, clamp, adhesive disc, kararya washer, soap, water, soft cloth, toilet paper or tissues, solvent and paper tape. Before the appliance that is already on the abdomen is removed, the one that is to replace it is assembled and the bottom opening is secured. Careful cleansing of the face-plate to remove all traces of oily substances, stool or lint is the next step. Medical solvents do this well but should be used sparingly with rubber plates. Then the protective paper is removed from one side of the adhesive disc and the sticky side is centered carefully over the opening in the face-plate and pressed to seal. Next, protective paper is removed from the other side of the adhesive disc and the karaya washer is moistened on one side with water to make it stickier. All these assembled components are set aside while the appliance being worn is removed. This can be done by gently pulling the adhesive surface away from the skin, although some patients prefer to drip solvent between the skin and the plate to dissolve the adhesive. After it is removed the patient may shower or cleanse the peristomal skin locally, using a non-creamy soap and a soft cloth. The area must be well rinsed to remove all traces of soap which would prevent sealing of the adhesive and is patted dry. With its moistened side to the skin, the karaya washer is centered around the stoma so that no skin at the stomal base is exposed. Finally the appliance is centered over the stoma and firmly pressed to secure the adhesive. Particularly if a belt is not worn, strips of adhesive paper tape around the edge of the face-plate to stick it to the abdominal skin can be used as additional security against accidental dislodgement.

Endless variations of this procedure are possible. It is conceivable that products from as many as half a dozen manufacturers might be used by a single person who has selected what is best for his particular needs.

As persons who have had ileostomy develop facility in placement of the equipment and care of the stoma, they can readily return to almost any kind of work and engage in whatever activities interest them, including active sports such as tennis, swimming and golf.

Ileostomy equipment is relatively expensive for people of modest income. For non-disposable appliances, the initial cost is $60 to $65. This includes two appliances, clamps, karaya washers, adhesives, solvents, deodorizers and cleaning supplies. The continuing expenses for most kinds of equipment—for replenishing supplies and occasional replacement of appliances—will average $12 to $15 a month. Since custom-made appliances cost more, it is best to try to use standard ready-made equipment.

Skin Problems

Skin problems are the plague of those who wear ileostomy equipment. The peristomal skin must be kept healthy for proper seating of the face-plate and this is not easily managed, for the area about the stoma is hidden from light, is deprived of the circulation of air, is continually coated with adhesives or other substances and occasionally is exposed to irritating fecal material.

Care of the skin usually is begun in the operating room, where a karaya washer is centered around the stoma and a temporary polyethylene transparent pouch with adhesive face-plate is applied to the skin. This equipment is removed daily so that the stoma and peristomal skin can be inspected. If the stoma heals well and skin integrity is maintained during the immediate postoperative days, fewer problems are encountered later on.

The most common skin problems are erythema and excoriation from exposure to stool enzymes, allergic sensitivity to adhesives or karaya, yeast infections (usually Candida albicans), pseudohyperepithelium, and the presence of mucosal implants.

It is difficult to give specific instructions for various combinations of problems, although first of course is constant reiteration of the importance of the directions previously given as to careful seating and sealing to avoid leakage. If excoriation develops, all irritating substances, including stool and adhesives, must be kept from the skin. A new "skin" to protect the excoriated area can be made by mixing karaya powder with antacid liquids and applying the paste in layers. Another method is to mix zinc oxide ointment with karaya powder until it has the consistency of peanut butter, then stir liquid glue into the mixture and butter the excoriated area with it. After the mixture is applied, a karaya washer with a 4-inch outside diameter is placed over it and the appliance then is used with a belt to hold it fast. The process is repeated every 24 hours until the skin is healed. If healing does not take place, suctioning the ileostomy continuously while exposing the surrounding skin to the rays of a lamp should be effective, although this entails special nursing around the clock. Aluminum acetate (Burow's) solution 1:20 used as soaks will also relieve excoriation if stool is not permitted to come into contact with the irritated areas. Surgical revision of a flush or retracted stoma may be necessary if stool cannot be kept from the skin. Often what is needed is a more convex face plate with a correctly tailored opening and careful placing of the karaya washer.

If a patient is sensitive to adhesive materials or karaya, as sometimes happens, substitution of another company's product for these substances may solve the problem. If a patient has had no skin irritation for months or years and then sensitivity suddenly develops, one must suspect that the manufacturer has changed a formula in his product.

Yeast infections respond well to mycostatin powder dusted very lightly over the affected skin, with the appliance removed every 24 to 48 hours for re-dusting. Since the powder may prevent the adhesive from holding securely, a belt may be worn during the seven to ten days it takes the skin to heal.

If repeated exposure to stool over a long period has caused the skin immediately around the stoma to thicken or elevate, correcting the convexity of the face-plate and the size of the opening may solve the problem and reduce the elevation.

Mucosal implants may have been left in the peristomal skin inadvertently when the stoma was being sutured to the skin. These implants weep and reduce the effectiveness of the adhesive. The cure is surgical removal.

Many a person with long established ileostomy has had minor problems with the stoma, skin or appliances over a period of time and has sought help from physicians, nurses, friends, surgical supply dealers and others. He may incorporate each new suggestion into his routine of ileostomy care. Often the result is that he will take hours to change an appliance and care for the peristomal skin, though the procedure should take only 15 to 20 minutes. Often in such cases, suggestions for easier care are simply not adopted; and perhaps if the method the patient is using is working for him, it is best to respect his methods.

Diet

The patient's diet after operation will be increased from "nothing by mouth" to bland low-fiber foods during the first seven to ten days in hospital. Then, if tolerance to the low-residue diet is good, fibrous foods may be introduced one at a time and any that do not cause nausea, abdominal cramping or increase in flatus may be included regularly until, in six to eight weeks, the diet is complete.

Milk products and orange juice often are not tolerated during the early weeks of convalescence, causing cramping and gas. Highly fibrous foods such as popcorn, corn on the cob, nuts, seeds, raw vegetables and fruits ought to be added last, and with caution, since they may cause mechanical obstruction. Fluid intake should be kept high, for the stool following operation is liquid, often with consequent reduction in urinary output that later may dispose to urinary calculi.

Chewing food well and swallowing slowly decreases the amount of air ingested and the formation of gas.

Stool Odor

Odor in the stool is directly related to the diet. Ideal effluent has a less offensive odor than feces, is dependent on diet, often has a sweet-sour smell similar to gastric juice and occasionally is fecal.[4] Some people complain of a plastic stool smell from the vinyl pouches. Fish, shellfish, and raw onions are the worst offenders, causing a very offensive stool odor.[5] Odor can be controlled by any number of commercial preparations. A few drops of a liquid or tablets containing substances related to the quarternary amines placed in the pouch are effective deodorants, although several may have to be tried before a suitable one is found. Crushed aspirin or chlorophyll tablets in the pouch seem to do as well in many cases[6] and they cost less. Since medications by mouth, such as chlorophyll, activated charcoal and bismuth subgallate, may increase the feeling of invalidism in people who have been ill a long time, they are best avoided.

Identifiable foods that appear in the ileostomy pouch may be a source of mechanical irritation to the bowel and a potential cause of obstruction. The most often seen particulate matter of this kind is corn, pea and navy bean hulls; tomato and green bean skins; lettuce leaves; orange, grapefruit and pineapple fibers; mushrooms, olives and nuts; dried meats such as salami and, occasionally, cooked egg white. If eaten in sizable amount and not chewed well, they may cause problems. Since resuming a full diet after operation is to be encouraged, instruction about careful chewing of these foods, then excluding from the diet only those that repeatedly cause dyspepsia, is the recommended course.[5]

Instruction of Patients

The surgeon's responsibilty is not only to cure disease but also to provide a means for adequate patient instruction regarding the altered method of toileting. As this can be most time-consuming, a nurse specialist with a relaxed attitude toward time can help the patient during this trying period. The patient—and his family too—must be given reassurance that the ileostomy will be only an inconvenience, not a tragedy. Discharge from the hospital is considered only when the patient can manage his ileostomy and equipment. He should be given printed instructions to take home with him.

Since care involves the physical, emotional and social needs of the patient and his family, close supervision is necessary and life-long professional guidance must be available. This involves a team of specialists and includes the surgeon, gastroenterologist, enterostoma nurse specialist or therapist, social worker, and dietician.

The visiting nurse can be a valuable asset and a volunteer from the United Ostomy Association can provide additional emotional support. In the period following discharge from the hospital it is important that the patient make frequent visits to the out-patient clinic for follow-up care and advice by both the surgeon and the enterostoma nurse. When the surgeon releases the patient to the gastroenterologist, visits to the enterostoma clinic at regular intervals are still indicated. Rehabilitation is complete when the patient has resumed an active, useful life in society.

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Medical Staff Conference

Refer to: Renal cystic disease—Medical Staff Conference, University of California, San Francisco. Calif Med 119:36-41, Nov 1973

Renal Cystic Disease

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

Dr. Smith:* *The topic for discussion at Medical Grand Rounds this morning will be that of renal cystic disease. Dr. Jerry Cooper will present the case of a patient with this disease.*

Dr. Cooper:† The patient is a 41-year-old married Caucasian wine salesman with multiple medical problems. He has polycystic kidney disease with chronic renal insufficiency, hypertension, hyperchloremic acidosis, nephrolithiasis, hyperuricemia, anemia and cardiomegaly. This morning we would like to focus the discussion on the problem of polycystic kidney disease. The patient was well until 1958, when he was seen by his private physician because of an episode of gross hematuria. At that time an intravenous pyelogram showed changes that were said to be compatible with polycystic kidney disease. He had a positive family history in that his mother also had polycystic kidney disease and died at age 44 of what was thought to be an intracerebral hemorrhage. None of his three children, all in their late teens, has been medically evaluated for the presence of polycystic kidney disease, but none has had hematuria or any suggestion of renal enlargement. From 1958 until 1964 the patient had one to three episodes of hematuria a year, usually lasting one day, and he had no other symptoms. He received no treatment during that time. In 1964 he was evaluated for left flank pain and hematuria which was attributed to passage of a stone. In 1970 he again had right flank pain and at that time passed what he described as "gravel," the composition of which proved to be mostly uric acid. When first seen at the University of California renal clinic in June 1971, he was found to have blood pressure of 190/140 mm of mercury, serum creatinine of 6 mg per 100 ml, blood urea nitrogen (BUN) of 80 mg per 100 ml, creatinine clearance of 14 ml per minute. The abdomen was distended and the kidneys enlarged and palpable. Control of hypertension was readily achieved with one gram of α-methyldopa (Aldomet®) per day and was sustained over the next several months.

In January and September of 1972, the occurrence of hematuria and flank pain were believed to result from either ruptured renal cysts or passage of stones, although no further stones have en documented. In November 1972, he was mitted with a two-week history of increasing akness and fatigue which had prevented his rking as a wine salesman. Blood pressure was 0/80. Serum creatinine was 10 mg per 100 ml d creatinine clearance was 7 ml per minute. He d pronounced acidosis, with plasma bicarbonate 12 mEq per liter. Arterial pH was 7.32, carbon oxide partial pressure (pCO_2) was 22 mm of rcury and oxygen partial pressure (pO_2) was 0 mm. The urinary pH was 6.

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†Jerry Cooper, MD, Resident in Medicine.

Although the question of renal bicarbonate sting had not been pursued in his earlier course, veral values of urinary pH of 7 had been re-ded earlier. Kidneys, ureters and bladder (KUB) owed a left lower pole renal calculus which had en present for several years and was unchanged position. Both kidneys were grossly increased size and a renal scan showed poor uptake bi-erally. The only treatment given during a five-y stay in hospital was sodium bicarbonate and uminum oxide (Amphojel®), and in that time eturn of muscle strength attended correction of dosis. Since discharge from the hospital the tient has returned to work and has continued to l well.

. SMITH: *Thank you, Dr. Cooper. This patient s referred to the hospital by Dr. Francis Bognino Berkeley. We have asked Dr. Curtis Morris to en the discussion concerning the problem of stic renal disease. Dr. Morris is Associate Pro-sor of Medicine and Pediatrics.*

. MORRIS:* The clinical story just presented like that of many adult patients diagnosed as ving polycystic kidney. Polycystic kidney is the m used to denote a variety of kidney disorders ich have in common the pathologic character-ic of cystic ectasia of the renal tubule. It is nically useful to divide polycystic kidney into ee general categories: classic polycystic kidney ease, medullary sponge kidney, and medullary stic disease (Table 1).

The most common kind of polycystic kidney is ssic polycystic kidney disease (hereafter re-red to as polycystic kidney) which is first ognized in adult life, usually in the fourth or h decade.[1] In the typical polycystic kidney of ult patients (type 3 in Potter's classification[2]) ssly cystic changes are apparent throughout

TABLE 1.—*Polycystic Kidney Disorders*

	Polycystic Kidney Disease				*Medullary Cystic Disease*		
	Adult	*Infantile*	*Renal Tubular Ectasia*	*Medullary Sponge Kidney*			
Pathological changes							
Cortex	cysts	cysts	ectasia	normal	dense fibrosis		
Medulla	cysts	cysts	ectasia	ectasia	cysts		
Decade diagnosed	3-4	1	1	3-4	1	1-5	2-3 (young adulthood)
Urographic abnormality							
Pelvocalyceal	+	−	−	−	−	−	−
Medullary opacification	−	−	+	+	−	−	−
Genetic transmission	autosomal dominant-sporadic	autosomal recessive	? autosomal recessive	sporadic	? recessive	sporadic	? autosomal dominant
Clinical characteristics							
Hematuria	+	−	−	+	−	−	−
Nephrolithiasis	−	−	−	+	−	−	−
Hypertension	+	±	occasionally	−	−	−	−
Pyelonephritis	+	−	−	+	−	−	−
Kidney size	enlarged	enlarged	normal	normal	−	small	−
Polycystic liver	+	+	+ hepatic fibrosis	−	−	−	−
Portal hypertension	occasionally	−	+	−	−	−	−
Functional characteristics							
Renal failure	+	+	− to mild?	−	+	+	+
Hyperchloremic acidosis	+	−	−	occasionally, classic RTA	occasionally, prox. RTA	occasionally, prox. RTA	−
Renal sodium wasting	−	−	−	−	+	+	+
Renal potassium wasting	−	−	−	−	+	+	−
Aminoaciduria	−	−	−	−	+	+	−
Usual Prognosis	Fatal	Fatal	Good—short term Uncertain—long term	Good	Fatal	Fatal	Fatal

+ = present — = absent

R. Curtis Morris, MD, Associate Professor of Medicine and iatrics.

the renal parenchyma, the cysts varying greatly in size. Microscopically, cystic ectasia of all tubular elements abounds. It is of note that the connective tissue is not particularly dense between the ectatic tubules. On the basis of extensive microdissection studies of such polycystic kidneys, Darmady concluded that the major and probably earlier cystic abnormality involves the medullary collecting duct, but clearly the cystic ectasia affects the cortical convoluted tubules as well.[3]

In most instances adult polycystic kidney disease is inherited as an autosomal dominant trait,[1] but the disorder also occurs without clear evidence of genetic transmission. As was true of the patient described this morning, gross hematuria occurs commonly in adult patients with polycystic kidney disease. The hematuria may occur in association with severe lower back pain or with no pain at all.

Polycystic kidney disease is one of the important causes of recurrent painful hematuria unassociated with nephrolithiasis. Symptomatic pyelonephritis occurs commonly in adult patients with polycystic kidney disease. Polycystic disease of the liver, a cystic ectasia of the bile duct radicles, frequently attends polycystic kidney and may result in hepatomegaly as striking as the renomegaly of polycystic kidney disease. The common symptom of abdominal fullness in patients with polycystic kidney is frequently a consequence of enlargement of both the liver and kidneys. In the great majority of adult patients with polycystic kidney disease, the cystic disease of the liver is of no functional or hemodynamic consequence. Only occasionally does it give rise to portal hypertension.

Progressive azotemia and uremia is characteristic of patients with polycystic kidney disease. Despite azotemia, impaired renal acidification may give rise to hyperchloremic acidosis, which can be severe in degree. That it is important to treat hyperchloremic acidosis is suggested by the recent clinical course of the patient just presented. Hypertension is a usual and often fatal complication of patients with polycystic kidney disease, and its onset can precede that of azotemia. Hamburger emphasized that strict control of hypertension can significantly delay the progression of renal insufficiency.[4] According to a recent retrospective study of 58 adult patients with polycystic kidney,[5] those patients with renal failure and hypertension died, on the average, 15 years earlier than those with renal failure and normal blood pressure. In patients who had intracranial aneurysm, which is a not infrequent accompaniment of polycystic kidney in adult patients, hypertension was attended by a similarly increased risk (in this case, of fatal rupture of the aneurysm).

In the characteristic intravenous urogram of adult patients with polycystic kidney disease, the overall size of the kidney is increased. According to some radiologists, the width of the renal parenchyma is predictably increased, as judged from that area bounded by the outer border of the kidney and the peripheral limits of the pelvocalyceal system. The pelvocalyceal system is frequently elongated, and the calyceal stalks can be so narrowed by impinging cysts that the pelvocalyceal pattern appears to be "stretched out" or "spidery." The routine intravenous urogram is, however, frequently not diagnostic in patients with polycystic kidney. Impressive claims have recently been made for infusion nephrotomography as the most predictably availing radiologic technique in diagnosing polycystic kidney.[5]

In the recent past, the prognosis of adult polycystic kidney disease has been dismal, death usually occurring within five to ten years of diagnosis. Prognosis has undoubtedly been improved by better control of hypertension, the greater availability of chronic dialytic therapy and renal transplantation. The analyzed experience, however, is not sufficient to make a very strong statement in this regard. A renal disorder apparently indistinguishable pathologically from polycystic kidney may give rise to no signs or symptoms throughout a normal life span. The finding of such renal disorders at laparotomy or postmortem examination is by no means rare.

Apart from indicating the obvious importance of patient selection in prognosis, the fact of a benign kind of polycystic kidney raises the important question of what confers a poor prognosis. One may speculate that a poor prognosis may not be predetermined by the intrinsic character of the renal disorder. Identification of specific determinants of progressive disease could, of course, have important therapeutic implications. Even when polycystic kidney disease is genetically transmitted as an autosomal dominant trait, there is no reason to suppose *a priori* that the causal genetic defect is of itself sufficient to compel expression of the cystic changes characteristic of polycystic kidney. These changes may require yet other determinants. That normally circulating substances may be required for the functional and structural expression of genetically determined renal disease is suggested by several recent observations.[6,7]

The term *medullary sponge kidney* (MSK) designates a renal disorder diagnosed by a urographic pattern quite unlike that described for classic polycystic kidney disease.[8-10] The diagnostic urogram (intravenous) has no characteristic alterations in outline of the pelvocalyceal system but rather by multiple discrete urographic opacifications clustered around, as if branching from, the calyceal "cups" of the pelvocalyceal system. The "characteristic" pyramidal urographic opacifications have prompted such descriptive imageries as "bouquets of flowers," "bunches of grapes," and "branching twigs of a leafless bush." Highly radiopaque calculi are often present at the pyramidal apices, and some radiologists consider their shape and grouping to be diagnostic. But nephrocalcinosis, indistinguishable from that seen in classic or "distal" renal tubular acidosis, occurs frequently in patients with MSK. The urographic pattern of MSK has been seen in successive generations,[10] but in most cases there appears to be no evidence of genetic transmission.

When originally coined by Cacchi and Ricci, the term *sponge kidney* was intended to connote enspongement of the urographic dye by the renal parenchyma: During the course of intravenous urography, the characteristic medullary opacifications appeared before the pelvocalyceal system was opacified.[8] Today, the term *medullary sponge kidney* is used to indicate only the occurrence, not the precedence, of urographic opacifications in the renal medulla. The term is usually explained as grossly descriptive of the spongy appearance of the tightly bunched cysts in the renal medulla that presumably account for the characteristic medullary opacifications.[10]

The most extensive pathological studies of MSK are those of Ekstrom et al[9] who, like Cacchi and Ricci, described gross cystic involvement limited to the renal pyramids. The kidneys are normal in size or only slightly enlarged. Grossly and miscroscopically, the most striking cystic involvement occurs at the apex of the renal pyramid. The cystic lesions are varied in size, shape and epithelial lining. The renal cystic involvement may be unilateral. The extent and severity of the cystic process may vary widely from pyramid to pyramid but characteristically spares the pyramidal base. Unlike polycystic renal disease, the renal cortex in MSK is free of cystic involvement.

The most common symptoms of MSK are those of urinary tract infection, hematuria and renal colic, which have been ascribed to pyelonephritis and nephrolithiasis. Expansion and rupture of the pyramidal cysts has not been invoked as a cause of the pain and hematuria. In contrast to adult patients with polycystic kidney (PCK), patients with MSK characteristically do not have hypertension or polycystic disease of the liver.

Hypercalciuria occurs frequently in patients with MSK.[9] This characteristic, the recently reported association of MSK and primary hyperparathyroidism,[11,12] and our awareness of this association of diseases in two additional patients suggest the intriguing possibility that primary hyperparathyroidism might be capable of causing a renal disorder urographically indistinguishable from MSK. In any case, in patients with MSK, particularly those with recurrent nephrolithiasis, it would seem prudent to consider the possibility of primary hyperparathyroidism, even in the absence of hypercalcemia. Classic (Type 1, distal) renal tubular acidosis occurs occasionally in patients with MSK.[10,13] The combination of renal tubular acidosis and hyperparathyroidism has not been described in patients with MSK. MSK has been described in successive generations of patients with Ehlers-Danlos syndrome, some of whom have also had renal tubular acidosis.[13] Although most patients with medullary sponge kidney do not have evidence of a systemic disorder of connective tissues, the occurrence of the association in a number of patients suggests the possibility that ectasia of the renal tubule can reflect a systemic disorder of connective tissue.

For a number of years the urographic pattern of medullary sponge kidney was considered to reflect a distinct renal disease in which the tubular ectasia was restricted to the medullary collecting ducts. It is clear now, however, that this is not the case.[10] In children the urographic pattern of medullary sponge kidney can reflect a kind of familial polycystic kidney in which both renal cortical and medullary tubules are ectatic.[14-16] This polycystic disorder appears to be pathologically akin to infantile polycystic kidney; but, in distinction from that disorder, the tubular ectasia is not frankly cystic, the functional impairment is slight and prolonged survival is characteristic.[15] For this not-so-cystic polycystic kidney, the term *renal tubular ectasia* (RTE) seems appropriate.[14] RTE is frequently associated with congenital hepatic fibrosis (CHF), a variant of polycystic liver in which the bile duct ectasia is not of frankly cystic magnitude, but in which dense perilobular fibrosis and symptomatic portal hypertension are characteristic.[14-16] In English children, according to Kerr, congenital hepatic fibrosis is the most common cause of portal hypertension unassociated with abnormalities of hepatic function such as reduction of albumin concentration and bromsulfophthalein (BSP) retention.[17] Children with CHF and portal hypertension are said to respond well to surgical shunting procedures.[16,17]

Medullary cystic disease (MCD) is a term used to describe a renal disorder characterized by rapidly terminal uremia and severe anemia without edema, significant increase in blood pressure, remarkable urine sediment or history of a clinical picture of pyelonephritis.[18,19] Although the cystic changes are limited to the renal medulla, the renal cortex is strikingly reduced in thickness and virtually replaced by dense interstitial fibrosis; many glomeruli are hylanized. The pathological changes described in MCD appear to be indistinguishable from those described in so-called juvenile nephronopthisis.[20] In both children and adults with MCD, there occurs the intriguing and clinically important phenomenon of renal sodium wasting. In this phenomenon, which apparently occurs only with advanced renal insufficiency, the urinary loss of sodium chloride is so great that severe extracellular volume depletion and hyponatremia can be prevented only with large dietary supplements of salt, sometimes as much as 25 grams per day.

It is not clear that the pathological changes described in MCD are those of a single distinct disease. In childhood the pattern of occurrence in affected siblings is consistent with autosomal recessive transmission, but clear-cut evidence of genetic transmission has not been reported. Although hypokalemia has been described infrequently in affected children, in each of three unrelated children with MCD studied by Dr. Elisabeth McSherry here at Moffitt Hospital, renal potassium wasting was striking and could be explained as a consequence of type 2 ("proximal") renal tubular acidosis.[21] In this disorder of renal acidification, a large reduction in the rate at which the proximal tubule reabsorbs bicarbonate results not only in bicarbonate wasting and "alkali-resistant" acidosis, but in the delivery to the distal tubule of such increased amounts of the relative impermeant bicarbonate anion that distal intraluminal electronegativity is increased, potassium secretion is thereby increased, and renal potassium wasting is promoted.

We and others[21,22] have found additional evidences of proximal tubular dysfunction in children with MCD such as glucosuria, aminoaciduria, and impaired tubular reabsorption of phosphate. Yet, in their study of two sibling children with MCD, Herdman and his coworkers[23] concluded that the proximal tubule was not affected. They demonstrated the absence of glucosuria, aminoaciduria and impaired tubular reabsorption of phosphate. On the basis of these and other physiologic characteristics, and from electron microscopic and microdissection studies, these investigators inferred that the "primary lesion" of MCD is in the distal tubule and collecting duct.

In a large kindred described by Goldman and his coworkers at Stanford, MCD occurred in young adults, and the pattern of occurrence in successive generations was consistent with an autosomal dominant transmission.[24] Because father-to-son transmission was not apparent, an X-linked genetic defect seemed possible. We have studied two brothers with the pathological findings of MCD in whom the renal disease was almost certainly inherited as an autosomal dominant trait. After a normal childhood and adolescence, both brothers had rapidly progressive renal insufficiency in their late teens. One died at 20 years; the younger had a successful renal transplant at age 21. The brothers' father and each of his three siblings, a male and two females, died of rapidly fatal renal failure between the age of 20 and 25 years. The brothers' paternal grandfather had died of renal insufficiency in early adulthood. The pathological changes described in the father's kidney are like those of MCD. Multiple first cousins of the proband have died of renal insufficiency in their late teens and early twenties. One first cousin died at the University of Iowa Medical School Hospital and was diagnosed at autopsy as having medullary cystic disease. We were able to study the proband's younger brother before the onset and during the course of progressive renal insufficiency. Tubular dysfunction did not occur until very late and was never remarkable. I am unaware of the occurrence of MCD in adult siblings except in the two kindreds discussed. Yet, sporadic MCD is not rare in an adult patient population, at least in that of a university hospital.

As currently characterized, MCD could be the final structural consequence of a number of different pathogenetic processes, some of which are genetically determined. With better definition of the physiological and biochemical characteristics of greater numbers of siblings with just detectable disease, it seems likely that a number of different renal disorders will be identified. Further, it seems safe to predict that specific determinants of expression and progression will also be identified. Perhaps in the future it will be possible to prevent or retard the development of medullary cystic disease by early, appropriate therapeutic intervention.

Trade and Generic Names of Drugs

Aldomet®	α-methyldopa
Amphojel®	aluminum oxide

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Important Advances in Clinical Medicine

Epitomes of Progress—Chest Diseases

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Chest Diseases. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Chest Diseases which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Chest Diseases of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, CA 94102

Fiberoptic Bronchoscopy

SINCE THE DEVELOPMENT of the flexible fiberoptic bronchoscope in the mid 1960's this instrument has rapidly become an important and useful tool in the diagnosis and treatment of pulmonary disorders.

The first clinical study reported passing the bronchofiberscope through a rigid bronchoscope or endotracheal tube. Subsequently the transnasal technique was described. Using the instrument through a rigid bronchoscope or endotracheal tube allows for easier removal and re-insertion of the bronchofiberscope. The transnasal method is performed under topical anesthesia with the seated patient. It adapts easily for bedside bronchoscopy and can be extended to patients with neck or mouth problems or to patients in whom the neck cannot be extended. This method has had very good patient acceptance without any increase in complication rate.

Several different bronchofiberscopes ranging in size from 3 to 6 mm in outside diameter are manufactured. All possess flexibility of the entire working length (usually about 55 cm), a remotely controllable tip and an aspiration channel (1 to 2 mm in diameter) which allows injection of anesthetic solution, aspiration of secretions or passage of brush or forcep biopsy instruments. The bronchofiberscope is illuminated by a cold light source (halogen or xenon). Cameras—motion picture, still picture, or videotape—can be attached to the eyepiece to record observations.

The remotely controllable distal tip can be flexed and extended to allow easy manipulation into all segmental bronchi, including those of the upper lobes. From the segmental level one gains visual access to several subsegmental branchings peripherally. Diagnostic accuracy is enhanced by the extended visual capability to areas previously inaccessible with the rigid bronchoscope. This increased diagnostic capability is magnified still further by the fact that transbronchoscopic brush and forcep biopsy instruments can successfully obtain adequate tissue specimens from these areas. Segmental bronchial secretions or washings following lavage with saline solution or water can be collected in a suction trap for cytology or culture. Additionally bronchography of the bronchial tree beyond the visual range can be accomplished by injecting contrast material through a catheter inserted into the aspiration channel of the bronchofiberscope.

Although the therapeutic value of bronchoscopy has been recognized for many years, the hazards and risks of performing the procedure frequently outweighed the benefits when applied in respiratory failure. By utilizing the bronchofiberscope in a "closed system" which allows continuous ventilation and oxygenation, therapeutic bronchoscopy can be applied effectively without complication through an endotracheal or tracheostomy tube. Tube placement, suctioning effectiveness, and airway patency can be immediately evaluated. Bedside therapeutic bronchoscopy by using the transnasal method has become useful in the patient with post-operative atelectasis who does not respond to intensive aerosol and chest physiotherapy.

Today, the fiberoptic bronchoscope has been established as an important tool in pulmonary medicine. On the horizon are developments in technique and instruments which will undoubtedly bring about even greater diagnostic effectiveness and therapeutic usefulness.

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Cardiovascular Function in Chronic Obstructive Lung Disease

EVIDENCE IS NOW ACCUMULATING that significant left ventricular, as well as right ventricular, dysfunction can occur in patients with chronic obstructive lung disease (COLD) in the absence of other causes for myocardial disease (for example, coronary artery disease, valvular disease, and hypertension).

Two patterns of cardiovascular dysfunction, as described by Burrows, et al, may be seen in moderately severe obstructive airway disease. Patients with clinical features of the "Type A," "pink puffer" form of COLD may have a "low output pattern" characterized by relatively normal arterial blood gases, decreased cardiac output, normal to increased pulmonary artery pressure, and increased pulmonary vascular resistance. Patients with the clinical features of the "Type B," "blue bloater" form of COLD are characterized by hypoxemia, hypercapnia, normal to increased cardiac output, pulmonary hypertension, and increased pulmonary vascular resistance.

Studies on left ventricular function in COLD by Baum, et al, demonstrated a high proportion of patients with elevated left ventricular end diastolic pressures and abnormal ventricular function curves, in the absence of other causes for left ventricular abnormality. The cause for the left ventricular dysfunction in COLD is not well understood and probably involves multiple factors, including acid-base imbalance, CO_2 retention, hypoxemia, and impairment of coronary artery flow and myocardial oxygenation secondary to increased cardiac chamber pressures.

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In-Hospital Use of Intermittent Positive Pressure Breathing Therapy

SOME 25 YEARS after the first use of intermittent positive pressure breathing (IPPB) as a therapeutic tool, controversy still rages around its applicability and value in the care of respiratory patients in hospital. In the care of outpatients, the pendulum seems to be swinging more and more *away* from at least the initial use of such devices, but not so in the hospital.

Though the pertinent literature is scant and the reported studies often anecdotal, carefully administered IPPB treatments with medication given at least three to four times a day, may (1) improve alveolar ventilation in some but not all patients, at least during the period of treatment, (2) mechanically dilate major airways permitting intermittent safe hyperinflation of the lungs, thus promoting clearance of secretions if coughing or suctioning thereafter is effective, (3) more effectively deliver therapeutic (bronchodilator and mucolytic) aerosols to distal airways in patients with reduced inspiratory force capabilities, and (4) reverse atelectasis in a certain number of patients where other means fail. (Note the cautious use of provisos in each of the above statements.)

Many criticisms of IPPB therapy are really criticisms of technique—for example, nosocomical infections, pneumothorax, adverse medication effects, decreased cardiac output, oxygen toxicity and arrhythmias. Other criticisms are blunted when one considers the now well-documented progressive deterioration in emphysema, the variable course of the other obstructive lung disorders, the very real problem of poor understanding of the limitations and hazards of IPPB devices, and the increasingly well-recognized disparity between tests of pulmonary function and *functionality* of the patient.

Many physicians have seen patients in whom bronchodilator aerosols were not effective when delivered by hand or compressor-driven nebulizers, who then benefited by the same medications administered by IPPB. Admittedly, many of these patients may have been poorly trained in the use of more simple aerosol generators, and the question of "psychological dependence" on the IPPB devices themselves certainly arises.

Adverse effects of IPPB therapy doubtless exist. A recent report supports our experience that some persons with particularly irritable airways (such as asthmatics) might respond to air under pressure with *increased* airways resistance, especially when no bronchodilators are used in the aerosol.

Over-utilization of IPPB in hospitals is a problem under increasing scrutiny by third party payers. In a recent review of 200 respiratory patient stays in our own hospital, where automatic IPPB stop orders are instituted after 72 hours, IPPB charges account for less than 10 percent of total hospital charges.

At present, a confusing and often contradictory literature notwithstanding, judicious and skilled use of IPPB in certain situations still seems to have merit, since the day when a truly controlled study of selected patients under therapy in hospitals, with and without such devices, seems a long way off. Such clinical investigation is urgently needed in light of increasing IPPB use in the hospital setting.

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Flucytosine, A Major Antifungal Agent

FLUCYTOSINE, marketed as Ancoban® (Roche), is the first new antifungal agent released to the profession in 15 years. While clinical usefulness has been limited to infections caused by cryptococcus neoformans and systemic candidiasis, the drug has established itself as a co-equal with amphotericin-B in these conditions. Its relatively low toxicity, administration by the oral route, and high sera and tissue levels, including the cerebral spinal fluid, make this an important addition to the armamentarium of the treatment of these mycoses, particularly in patients where amphotericin cannot be used.

The action of this antimetabolite, a derivative of cytosine, appears to be selective interference with metabolic pathways in certain microorganisms. Observed toxicity has included neutropenia, thrombocytopenia, and dose-related hepatic dysfunction. These have all been mild and reversible.

Resistance to the organism has been seen to emerge, especially when smaller doses have been used.

Combined or alternating courses of therapy with amphotericin-B appear promising and are under investigation.

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Alpha$_1$-Antitrypsin: What's in It for the Patient?

CURRENTLY THERE IS NO WAY to arrest the progress of emphysema in patients who are deficient in alpha$_1$-antitrypsin. People who are homozygotes for the "zz" deficiency genes tend to get emphysema at an early age. While the exact incidence of emphysema in homozygotes is unknown, 95 percent of those who are found by proband studies or by referral from other physicians eventually develop emphysema. The average age of onset is about 35 years and in one large study 90 percent showed clinical effects of the disease by age 50. Once the disease has started it often pursues a relentless downhill course characterized by dyspnea and variable amounts of cough. Expiratory flow limitation can be accounted for by loss of lung elastic recoil in about half of the patients; in the other patients, airflow limitation is due to both loss of lung elastic recoil and intrinsic airway disease. Clinical evidence of chronic bronchitis does not serve as a useful predictor of the pattern of airway obstruction.

The evidence that emphysema occurs with increased frequency in heterozygotes is controversial, and the question cannot be settled from the available literature. Some observers have suggested that cigarette smoke or other pulmonary irritants may be important factors in the speed and severity of development of the disease in heterozygotes and homozygotes but these suggestions are unproven.

In light of our limited knowledge, all we can offer these patients at present is genetic counseling, advice about elimination of irritants, and the usual therapy of emphysema. However, studies on the biochemistry of alpha$_1$-antitrypsin offer some hope that it may be possible to design a drug to replace the missing protein. With some luck such a drug may prevent the emphysema which develops in these patients.

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Hypoxemic, Hyperventilatory Respiratory Insufficiency:

A Common Post-operative Complication

WITH THE ADVENT of modern surgical techniques the morbidity and mortality associated with the intra-operative period has considerably declined. The post-operative period, however, is still fraught with many and diverse hazards, not the least of which is a fairly recently appreciated entity—hypoxemic, hyperventilatory respiratory failure. By definition this condition is associated with a PaO_2 below 60 mm of mercury, a $PaCO_2$ below 35 mm of mercury and a variable arterial pH. No patients or types of operation are immune. The etiology is multifactorial and may include one or a combination of the following: (1) Excessive intravenous fluid administration, (2) microscopic pulmonary emboli of clotted material or fat, (3) excessive supplemental oxygenation without ample humidification, (4) atelectasis, (5) anesthesia, (6) respiratory infections, (7) shock and (8) aspiration. These varied insults find expression at the pulmonary level as: mucociliary dysfunction; surfactant loss; macrophage disintegration; alveolar fluid filling and collapse; fluid and protein deposition in the alveolar capillary interstitium; and abnormal capillary blood flow and distribution. The physiologic expressions of these anatomical abnormalities are an abnormal distribution of both ventilation and perfusion, a decrease in lung compliance, an increase in airway resistance and a pronounced increase in the work of breathing—all manifested clinically as tachypnea, decreased tidal volume, hypoxemia, hypocapnia and a variable arterial pH.

Since this type of respiratory insufficiency has multiple causes, it would seem easier to prevent their occurrence than to correct them after the fact. This being so, *anticipatory* and *prophylactic* treatment would seem indicated. Thus, fluid and electrolytes should be carefully monitored particularly with an eye to preventing excess fluid loads; operative ventilatory support should not lead to under-ventilation or over-ventilation; anesthesia should be properly selected and carefully used; well humidified oxygenation should be appropriate to the patient's clinical situation; relief of pain should be accomplished with the least possible amount of analgesic, and pulmonary toilet and intermittent positive pressure breathing should be employed early and frequently. The patient's clinical condition should be followed at least daily by bedside tidal volumes and vital capacities, respiratory rates, physical examinations and arterial blood gases. If all these means are employed, hypoxemic hypocapnic ventilatory failure should decrease in frequency.

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Early Diagnosis of Chronic Obstructive Pulmonary Disease

SINCE THE ADVANCED STAGE of the chronic obstructive pulmonary diseases (emphysema, chronic bronchitis, chronic asthma, rarely, bronchiectasis) appears to follow a relentless and progressive course regardless of treatment, increasing attention has been directed to early detection. Efforts are under way to screen large populations for alpha$_1$-antitrypsin deficiency to detect high-risk individuals. Other workers are using newer screening pulmonary function tests to detect asymptomatic persons with early disease that still may be reversible. These results suggest that airway obstruction can be detected before it causes symptoms, and also that it is possible to differentiate one type of airway obstruction from another.

Even when the usual tests of pulmonary function are normal, airway obstruction can be detected by an abnormal decrease in maximal airflow rates, especially at low lung volumes. The association of a decreased single-breath CO diffusing capacity suggests a loss of alveolar-capillary surface area (for example, emphysema). A normal diffusing capacity in the presence of airway obstruction suggests intrinsic airway disease. The specific type of airway disease may be defined by tantalum bronchography and pulmonary function tests in which airway resistance and maximal airflow rates are related to lung elastic recoil pressure. Finally, when all other pulmonary function tests are normal in an asymptomatic person, the "closing volume" may still be abnormally increased. This may indicate obstruction in the very smallest airways, less than 2 mm in diameter. If these different types of chronic obstructive pulmonary diseases can be detected early, preliminary studies suggest that therapeutic intervention may correct functional abnormalities; whether the disease itself is arrested or reversed remains to be seen.

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Corticosteroids in the Treatment of Adult Respiratory Distress Syndromes

WHEN PATIENTS have experienced prolonged shock due to sepis, hemorrhage, or following severe trauma, certain morphologic alterations in the lung are potential consequences. These may include intravascular platelet aggregation, sequestration of polymorphonuclear leukocytes with resultant release of lysozomal enzymes from these cells onto the pre-capillary arteriolar and capillary walls, and attenuation of pulmonary surfactant. These changes then lead to vascular constriction with leakage of plasma fluid into the pulmonary interstitial spaces. The end result of these well known changes is the development of functional alterations in pulmonary gas exchange characterized by progressingly increasing hypoxemia and hypocapnea. Some of these same findings have also been described in pulmonary aspiration, smoke inhalation, and fat embolism.

The administration of high pharmacologic doses of corticosteroids has been suggested as desirable in preventing progression of the morphologic changes in the lung. They are thought to be particularly helpful in shock due to sepsis or hemorrhage, in smoke inhalations, or in aspiration pneumonia. Whether or not they are truly effective in adult respiratory distress syndromes of all types has not been conclusively established.

In order to be effective, the following dosage schedules have been recommended: Methylprednisolone 30 mg per kilogram of body weight or dexamethasone 6.0 mg per kilogram given either as a single bolus intravenous injection or repeated every eight hours for up to 72 hours.

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Reversed Aorta to Saphenous Vein Grafts

WHEN THE CORONARY ARTERIES become occluded by atherosclerosis so that chest pain upon exertion, emotional reaction or after the ingestion of a large meal intervenes at regular intervals (stable angina) and does not respond to medical management, it is now an acceptable procedure to subject such patients to a series of studies including ventriculography and ciné coronary angiography. If they are found to be satisfactory candidates from all points of view, myocardial revascularization can be carried out by aorta-to-coronary vein grafting. Recent studies have indicated in-hospital mortalities of less than 7 percent throughout the country for single and double grafts and of 8 percent for triple grafts. Such experienced institutions as the Cleveland Clinic report a 1.2 percent mortality. Combinations with other revascularization procedures such as internal mammary-to-coronary anastomosis and internal mammary artery implantation have mortality rates similar to those of vein grafts alone, as does conventional coronary endarterectomies in certain selected cases.

Pre-infarction angina (Sampson's angina) is now also considered an indication for immediate myocardial revascularization. This differs from stable angina in that the chest pain lasts longer, has either not been present formerly or has changed in nature from its former pattern and is associated with transient changes in the T-wave patterns and the ST segment patterns without evidence of Q-waves in the electrocardiogram combined with an absence of changes in the enzyme laboratory findings characteristic of damage to the myocardium.

Angina inversis, which has been associated roentgenologically with the presence of a single coronary arterial occlusion, particularly of the anterior descending or coronary spasm, and has the clinical picture of the patient awakening at night with characteristic anginal pain not present during the daytime, does not respond to coronary revascularization as do the other two types.

After myocardial infarction has occurred, revascularization procedures do not seem either to reverse the course of the evolution of the disease or to decrease the mortality rates. Hence they cannot yet be recommended except in certain select instances where excision of an aneurysm or closure of a ventricular defect secondary to the infarction will save an otherwise rapidly deteriorating situation.

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Drug Therapy in Asthma

DESPITE GREAT ADVANCES in the understanding of the immunology and other aspects of asthma, drug therapy remains the most important therapeutic means available for relief of bronchospasm. For treatment purposes it is convenient to consider several, usually distinct, clinical presentations of asthma: combinations of mild, severe, intermittent and persistent.

Mild intermittent disease responds well to almost any therapy including inhaled adrenergic drugs, oral adrenergic or aminophylline preparations or both, or the simple avoidance of precipitating factors. Mild persistent bronchospasm is best treated with oral adrenergic or aminophylline preparations; inhaled bronchodilators should be avoided in this condition. Cases of persistent asthma which do not respond satisfactorily to oral adrenergic or aminophylline preparations or to combinations of them are candidates for oral corticosteroids given in low dosage and preferably in short courses or, if necessary, for longer periods, every other day. The usual safeguards of tuberculin skin testing and evaluation of ulcer and diabetic potential must be followed before beginning corticosteroid therapy.

Severe and life threatening asthma is best treated in a hospital setting with large amounts of intravenous fluids, parenteral aminophylline, and costicosteroids in high dosage (but for a short period). Frequent blood gas analysis and capability for intubation are essential.

The Federal Drug Administration has recently released sodium cromoglycate for use in this country. Other promising drugs are salbutamol and terbutaline.

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Surgical Treatment of Hiatal Hernia

RECENT MODIFICATIONS in operations for hiatal hernia are based upon pressures and acid reflex studies that have shown that an essential part of the repair mechanism is: (1) the prevention of acid reflux into the esophagus and (2) the lowering of the gastro-esophageal junction below the diaphragm where, due to normal pressure relationship, it regains its sphinctorial function.

The Nissen fundoplication involves an infolding of the upper portion of the stomach around the esophagus for 2 or 3 centimeters. The somewhat similar Belsey operation constitutes a fundoplication around the esophagus without a complete circle being accomplished but still bearing the esophagus in a full 2 or 3 centimeter length of tunnel. Normally these procedures are carried out through a chest incision although surgeons skilled in upper abdominal operations can perform them equally well, with an upper abdominal incision reflecting the left lobe of the liver.

The Hill procedure involves gastroplexy of the esophageal gastric junction just below the arcuate ligament of the diaphragm, where the fibers of the diaphragm are tendinous in character, and this keeps the gastro-esophageal junction firmly fixed below the diaphragmatic crux. Concomitant vagotomy and pyloroplasty are added only in those patients who have had, in addition to the hiatal hernia, duodenal or gastric ulcers or an extremely high titer of acid reflux. Strictures of the esophagus resulting from hiatal hernia in a great majority of instances heal themselves after repair of the hernia. They occur at the columnal squamous junction rather than at the gastro-esophageal junction and in those cases which do not spontaneously heal, a few esophageal dilations are generally sufficient to overcome the narrowing of the esophagus provided the hiatal hernia repair is adequate.

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Lung Oxidant Toxicity

IN CERTAIN EXPERIMENTAL and clinical situations inhalation of oxidants, including both oxygen at tensions considerably above ambient levels and the pollutant oxidants (ozone and oxides of nitrogen) leads to "diffuse bronchio-alveolar damage." Although temporal pathological studies of oxidant-induced lesions in man are meager and the relationship of pulmonary O_2 cytotoxicity to the toxic effects of pollutant oxidants is still unclear, available studies indicate that excessive oxidant exposure causes damage to bronchial mucosa, alveolar epithelium, and capillary endothelium resulting in bronchio-alveolar inflammation and edema. The precise time-dose relationship for the three oxidants is not well defined in man. Experimental and clinical observations suggest a wide range of species and individual susceptibility or resistance to oxidant damage. In addition, tolerance and cross-tolerance to a toxic oxidant level after prolonged low-dose or acute intermittent-dose oxidant exposure has been noted. Although the critical mode of interaction between oxidants and lung cells is still unclear, excessive oxidant exposure can be expected to cause loss of cellular reducing equivalents and unsaturated lipid oxidation, presumably via free radical mechanisms.

Oxidant damage occurs coincident with oxidant interaction with lung cellular oxido-reductive processes and inactivation of enzymatic thiol groups. Recent studies have suggested that the lung contains a reservoir of thiol protective substances (for example, glutathione) and that this reservoir can be compromised or augmented under certain conditions . . . a function of oxidative-protective thiols analogous to those of erythrocytes. Further studies have emphasized the presence in lung tissue of oxidant detoxification mechanisms that potentially function to dissipate the toxic products of lipid peroxidation. Indeed, in tolerance-producing situations these mechanisms show an augmented ability to detoxify lipid peroxides via the glutathione peroxidase mechanism.

Lung enzymatic adaptations may determine lung resistance to oxidant damage . . . increased oxidant levels may induce an augmentation of these lung antioxidant defense mechanisms. Biochemical studies of tissue may be a simple but sensitive indicator for detecting lung oxidant damage. Although current studies are not sufficient by themselves to lead to a unitary version of lung oxidant damage, they indicate a clear program of experiments to test the significance of oxidant induced lung metabolic pertubations and suggest mechanisms of potentially treating these syndromes.

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EDITORIAL

The Overlapping Spectrum of Radiologic Signs in Chronic Ulcerative Colitis and Crohn's Disease of the Colon

EVER SINCE Marshak, Wolf, and Eliasoph[1] described the radiologic signs of Crohn's disease of the colon, which they called segmental colitis, concentrated efforts have been made by radiologists to establish definitive criteria for the differentiation between that disease and chronic ulcerative colitis. In 1966, Marshak and Lindner[2] wrote the article that further defined the signs and made the distinction easier in most instances. The two classic articles by Lockhart-Mummery and Morson[3,4] established the basis of differentiation for the pathologist and confirmed and further supported the radiologic interpretation of Marshak and his associates.

Because the radiologic and histologic findings conformed to the typical clinical course of these diseases as they appeared in the great majority of patients, it seemed that what was needed for diagnosis was only a strict application of the criteria, and perhaps addition of some further refinements to increase their accuracy. Clinicians, radiologists and pathologists continue to have difficulties, however, in making a diagnosis in many patients, and articles on differential signs of chronic ulcerative colitis and Crohn's disease continue to be written.

Glotzer and his coworkers,[5] using histologic criteria to differentiate between these two forms of colitis, found an overlap in about one fourth of the patients they studied. A similar overlap was encountered by Schachter and his associates,[6] who concluded that histologic interpretations are not the absolute criteria for diagnosis if they are opposed by clear-cut clinical and radiologic findings. Margulis and his associates,[7] in a study of the radiologic findings in 150 histologically proved cases of either chronic ulcerative colitis or Crohn's disease of the colon, found the diagnostic accuracy of three gastrointestinal radiologists to be between 70 and 79 percent. It is interesting that, although these three groups of investigators used different approaches, they all arrived at approximately the same results: In about one fourth of their cases, the diagnostic criteria used by them failed to distinguish the two forms of colitis. This really is not surprising because the causes for the two diseases have not been established. The two conditions may embrace a number of yet-unidentified diseases, or they may really represent one disease that has a wide spectrum of manifestations. There are, however, radiologic signs, as G. W. Friedland points out in this issue of CALIFORNIA MEDICINE, that are generally reliable in establishing the diagnosis of Crohn's disease if only these two forms of colitis are considered, and not other inflammatory diseases of the large bowel. These radiologic signs are deep ulcers, sinuses, fistulas, and a narrowed and ulcerated terminal ileum. None of these signs, however, are absolutely accurate.

Goldberg, Carbone, and Margulis[8] have shown that the radiologic appearance of ulcerative colitis can change with treatment. Nelson et al[9] demonstrated that, at various stages in the same patient, the radiologic appearance of the colon may change, whether the patient is afflicted with chronic ulcerative colitis or Crohn's disease. Margulis et al[7] found fistulas in a small number of patients who had chronic ulcerative colitis. Even the terminal ileum in patients with Crohn's disease may appear normal by rigorous radiologic criteria and yet be found to be involved at resection.[10]

Using all signs together, the radiologist, like the clinician and the pathologist, is still diagnostically accurate in about three-fourths of the patients. It becomes, then, a question of attitude—whether one emphasizes the fact that it is possible to make the diagnosis in 75 percent of cases or laments the chance of 25 percent error.

Considering the present stage of knowledge about the nature of the two conditions, even the 75 percent accuracy is impressive.

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"Prolixity Will be Construed as Uncertainty"

IN THE ERA of essay examinations, the warning, "Prolixity will be construed as uncertainty," was sounded before all of our anatomy examinations in our first year in medical school. The exhortation comes to mind now as we attempt to review the published reports on septic shock. Since the initial article on bacteremia due to enteric Gram-negative bacilli other than salmonellae came from the University of Minnesota in 1951,[1] there has been a major investigative effort to elucidate the pathophysiologic features and to develop rational and effective therapy for shock associated with bacteremia. Among the investigators, Doctors Weil and Shubin have been leaders, Doctor Weil's interest having been kindled in his early years at the University of Minnesota.

Interest in Gram-negative bacillary bacteremia has become widespread not only because of the recognition of the problem, but also because the frequency of such infections is increasing.[2] For example, at one university hospital where the average daily census is 300 patients, there are 200 cases of bacteremia due to Gram-negative bacilli annually, with a mortality of 34 percent.[3] The frequency of Gram-negative bacillary bacteremia varies from hospital to hospital, but a prevalence of 0.8 percent of admissions is not uncommon. If this figure is projected to the 32,895,000 patients discharged from general hospitals in the United States in 1971, approximately 260,000 cases of Gram-negative bacillary bacteremia can be expected per year in the United States. The fatality rate varies between 20 and 50 percent. Assuming an average mortality midway between these values, 91,000 deaths per year may be attributed to Gram-negative bacillary bacteremia.

Against this background, the prevention and treatment of "Gram-negative" or "endotoxic" shock is a subject of major importance to all physicians. The review by Weil and Shubin which is published elsewhere in these pages summarizes current approaches to the treatment of patients with bacteremic shock which have been drawn from their careful and extensive physiological studies at the Shock Research Unit. All physicians should read this review. While the suggestions are not above controversy, Weil and Shubin have avoided being dogmatic, have emphasized the basic generalizations with which almost all clinicians agree, and have indicated the areas in which clear proof of therapeutic efficacy of a given regimen is lacking. The generalizations with which there is almost complete agreement include: sound surgical principles, such as draining of loculated pus, must be applied in the treatment of infections; early initiation of appropriate systemic antibacterial therapy is essential; and measures should be directed at the improvement of oxygenation at the cellular level. The fields of controversy include the value of corticosteroid drugs and of anticoagulation, vasopressor and vasodilator drugs.

However, as Weil and Shubin point out, even with modern tools of applied clinical physiology to correct circulatory collapse, the incidence and mortality of "Gram-negative" shock remain high. Emphasis must be directed at prevention, since many of these infections are acquired as a consequence of procedures which are considered by many physicians as minor, benign and routine, and as such are overlooked as important potential sources of Gram-negative bacillary bacteremia. Such procedures include the prolonged use of indwelling venous catheters, failure to employ properly closed urinary drainage systems, the use of ventilatory therapy equipment which has not been decontaminated and the application of substances such as soaps, creams and ointments which may be contaminated with bacteria.

The length of these comments should not be construed as reflecting the breadth of the problem, but rather the continuing uncertainty about optimal methods for prevention and management of Gram-negative bacillary bacteremia. Perhaps with further clinical investigation, particularly in the areas of prevention through modification of the host[4,5] or the environment, a future editorial may be as brief as "veni, vidi, vici."

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Informed Consent in Focus

THE LEGAL CONCEPT of "informed consent" has been thrust upon the medical profession rather precipitously and, for many physicians, without warning. To act and react intelligently and in the best interest of both patient and physician, several vital points need to be in focus.

1. "Informed consent" did not develop in a vacuum. For at least a decade in the United States and elsewhere the protection of the individual against the giants of mechanized and computerized society has been promoted, developed and imposed upon all. This protection, under the general label of "consumerism," manifests itself in many ways. Essentially, it is a revolt against mass advertising, mass production, mass distribution, mass everything. It has taken root and it is flowering. It has been said that consumerism is a magic word in contemporary society.

A basic concept of consumerism is that every individual has a "right to know" and a right to make his own decision, uncoerced by television or any other overpowering, brain-washing technique. The legal doctrine of informed consent is one among hundreds of manifestations of the concept of the right to know and to make one's own decisions, good, bad or indifferent. To understand what the courts are saying on informed consent, one must relate the concept to the whole —the whole being protection of the individual.

2. While the legal requirement of informed consent in medicine is stated in terms of telling the patient about risks and alternates, there is nothing in the law or in the concept of informed consent that mandates presentation of a negative or fear-provoking approach to the patient. In *Cobbs vs. Grant* the California Supreme Court held that a legally valid consent requires that the physician convey all information necessary for the patient to make a knowledgeable decision. Although to date cases before courts have involved issues that have resulted in an emphasis on the negative aspects of the "tell it like it is" rule, the patient's right to know includes all essential information; in other words, the positive as well as the negative, the benefits as well as the risks. Therefore, in approaching application and implementation of informed consent on a real life physician-patient basis, it would appear essential for the physician to give equal billing to the benefits of a procedure—to the good that it may do and the reasons it is recommended.

3. There is nothing new in the requirement of consent to any procedure that involves bodily contact. Without consent, any bodily contact that involves possibility of harm is an assault or battery. Hence, consent, express or implied, has always been necessary to elective surgical procedures and to other procedures involving bodily contact. The newness is in the word "informed." The concept that the patient has a right to know, coupled with a right to make his own decision on the basis of knowledge, is the new development. This, however, changes traditional concepts. No longer does a printed form suffice. It neither implies nor proves that the signer had any information whatsoever. No longer can the task of obtaining consent be routinely delegated to aides and assistants. In *Cobbs vs. Grant* the California Supreme Court made it very clear that informing the patient is the duty of the physician. Consent without adequate information on which to form a judgment is no longer legally sufficient. The Court also said a patient may decline information. This is fine if

the decision and the expressed wish not to be informed originate solely with the patient, but is a slender reed indeed if suggested or stimulated in any way by the physician.

4. What should the physician do now to obtain a legally sufficient consent? First, he must develop methods suitable to him and his practice to acquaint patients with the benefits, risks and alternates to procedures that involve bodily contact, hence requiring consent. Any method that will achieve the legally required objective is acceptable. The use of specially prepared booklets or monographs can be a desirable tool in many instances. In other situations perhaps spoken communication will be the most satisfactory. The task of "informing" does not lend itself to mass production. In addition to developing information techniques, the physician needs to understand what will give him the most protection in a court of law. First, the signature of the patient on any paper is not necessarily helpful. Signature on an explanatory document that is written in plain English, is of some help; signature on a complicated instrument, cast in stilted medical or legal terms, is most likely useless and possibly harmful. Probably the most helpful to the physician is his own entry in his record of the patient, entered as soon as possible after making the explanation and securing consent. The entry should briefly summarize the discussion with the patient and identify the patient's basic responses. As a "record made in the ordinary course of business," it is entitled to great weight.

5. Why bother with an "informed consent"? Clearly, if the medical management of a patient results in a satisfactory conclusion, the presence or absence of an informed consent is highly unlikely to surface. On the other hand, if a bad result occurs, the absence of an "informed consent" can be the ground on which a malpractice suit is constructed, even though the medical or surgical care furnished was of top quality and in nowise negligent. The real impact of the doctrine of informed consent on the practicing physician is that it creates a new and additional framework for a malpractice suit. Total absence of consent has always been the ground for an assault and battery complaint; but now a consent obtained, but without adequately informing the patient, though it may protect against an assault and battery suit, will not protect against a suit based on lack of "informed" consent.

The requirement of informed consent is not all bad. Various studies have demonstrated that the patient who refuses risky surgery when the risks are explained is also quite likely to be the suit-prone patient. So perhaps implementation of the informed consent concept may prevent some malpractice suits that would otherwise have occurred. Be that as it may, one thing is certain and that is that the plaintiff's lawyers will allege lack of informed consent as a routine matter in future malpractice suits.

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From "Crisis" to Chaos to What?

THE FLAMES of what has been officially declared a "crisis" in health care have been burning more or less out of control for more than a decade. Each effort to contain or extinguish them seems to end up by just adding more fuel to the fires. It is worth remembering that this has been for the most part a government-determined and government-declared "crisis," and it is worth noting that wave after wave of government plans and programs have done little to improve things and more often seem to have made them worse. There is much to suggest that, if present trends continue, what so far has been merely a "crisis" may soon become some sort of chaos.

Of late there seems to have been less talk of crisis and more evidence of chaos. The problems of the health care crisis reflect many of the unsolved problems of government and society generally. There seems to be a growing resistance to regulation or control by government or by any outside authority, possibly because these simply are not working well in today's society. The "crisis" in health care began by focusing particular attention on health care and longevity, and those in government who were assigned to deal with this crisis seem to have assumed that, if enough money were available and properly allocated, health and long life could become the right of every American.

The miscalculations were little short of monumental. The infusion of money produced rising costs in patient care which largely negated the desired effect of providing vastly more services for vastly more people. The regulations which had to be developed turned out to be discriminatory, costly in themselves and also largely defeating of the intended purpose. The thesis that medical services and their costs could be reduced by greater emphasis on prevention is proving to be an illusion. People simply do not behave as though they wanted to live forever, until after they get good and sick. And recently the courts have joined the administrative and legislative branches of government in their efforts to regulate and control the health care "crisis" by adding the dimensions of a legal adversary encounter to every contact between a doctor and his patient. The overall result of all this may not exactly be "chaos" but it seems awfully close to it.

It is to be hoped that this chaos will turn out to be more apparent than real. One is reminded of a chrysalis, where the chaos is surely more apparent than real, and where something good comes of it. But it seems unlikely that the present approaches to either the crisis or the chaos are likely to be very much more effective in the future than they were in the past. The track record of decision-making by government, and the examples of government-operated medical services which do not even attempt to meet the criteria that are expected of others is not reassuring, and it seems that the time has come when no segment of society, including government, can plan for every other segment of society, tell it what it will or will not do, and make it work.

It is therefore suggested that in this modern interdependent, yet still independent society, new approaches to problem-solving and decision-making are needed. Somehow those who must make it work must become more directly involved in deciding what is to be done and how they will do it. In medicine and health care, this means not only government, and the consumers (whose involvement is already accepted and sometimes even mandated), but the whole spectrum of providers who must make it work must participate effectively in the decision-making process which determines what is to be done. Physicians are in a peculiar dual role since they must represent patients as well as themselves. Physicians are most aware of the whole spectrum of patients and their needs and can best represent patients although they will always be accused of self interest. Legislators, administrators and even consumers cannot really represent patients since they are generally healthy and generally have had little contact with significant numbers of patients. Fortunately there is no fundamental conflict for the physician, since it is fundamentally true that what is best for the patient is always in the long run best for the physician.

In this state of affairs, medicine should press with some vigor for new approaches to problem-solving in health care with broader representation of all who should be involved in decision-making. The physicians involved should be well versed in what the problems are. This is clearly necessary if there are to be rational and practical resolutions of either the crisis or the chaos.

—MSMW

CASE REPORTS

Refer to: Brown MJ, King RM, Bruner CW: Congenital side-to-side tracheoesophageal fistula in the adult. Calif Med 119:54-55, Nov 1973

Congenital Side-to-Side Tracheoesophageal Fistula in the Adult

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ALTHOUGH IN MOST reported cases of congenital tracheoesophageal fistula the patients have had accompanying atresia of the esophagus, in an occasional case the lesion is side-to-side or H-shaped without atresia.

Reports on the few patients with this form of fistula who have lived to adulthood indicate that they suffered from cough, choking, chronic respiratory infection, and varying degrees of invalidism unless the lesion was surgically corrected.

We have found reports in the literature of 11 adults with congenital tracheoesophageal fistula without atresia (Table 1) and the case here reported brings the total to 12.

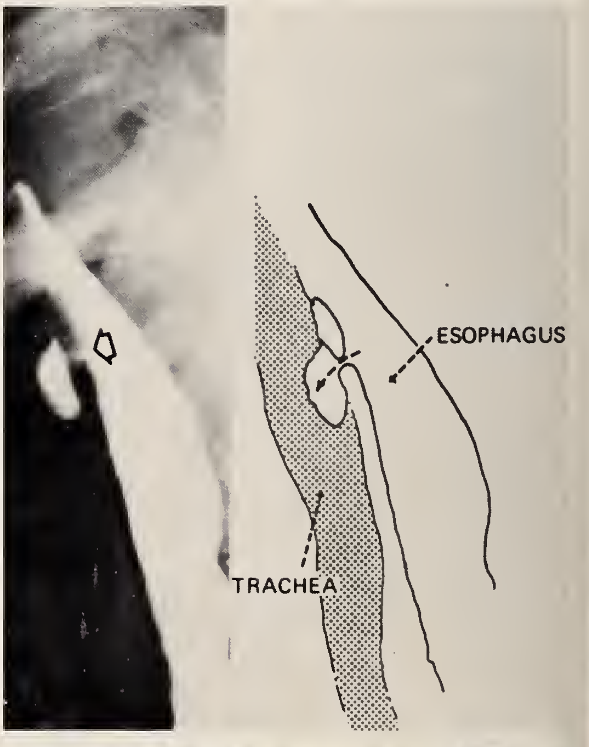
Report of a Case

The patient, a 41-year-old white man, gave a history of repeated attacks of pneumonia and chronic respiratory infection since infancy. For many years he had had a cough productive of from 15 to 30 ml of sputum daily. There had never been any findings of tuberculosis or fungus infection.

The man was underweight, but except for rales at the lung bases no other abnormalities were noted. Routine laboratory tests, including sputum studies for tuberculosis and fungus organisms, were negative. Chest films showed increased basal markings and slight deviation of the trachea to the left. A barium swallow with the patient prone showed a tracheoesophageal fistula just below the thoracic inlet (see illustration). After the fistula was demonstrated by these studies, the tracheal and esophageal openings were seen by endoscopy. Bronchograms did not visualize the fistula, however.

The chest was opened through the left fourth intercostal space, in view of the fact that the trachea deviated somewhat to that side. The fistula lay between the trachea and the anterior aspect of the esophagus at the level of the third dorsal vertebra. The fistulous tract was exceedingly short because of the apposition of trachea and esophagus.

The fistula was divided, and the tracheal opening was closed with a single layer of fine silk sutures. The esophagus was repaired with a row



Lateral view of esophagus with barium passing into trachea through tracheoesophageal fistula.

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*Deceased.

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Submitted March 6, 1973.

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TABLE 1. — *Data on Recorded Cases of Tracheoesophageal Fistula in Adults*

Author, Date	*Age and Sex*	*Symptoms*	*Method of Diagnosis*	*Location of Fistula*	*Treatment*
Eppinger[1] 1880 ..	"Young" M	Unknown	Autopsy	Just above carina	None
Widmann[2] 1921 ..	34 M	Chest disease, 14 years	Autopsy	10th tracheal ring	None
Negus[3] 1929	45 M	No symptoms from fistula; died of cancer of lung	Autopsy	Not clearly stated	None
McKinney[4] 1933 ..	58 F	Vomiting, cough, and expectoration of food	Barium swallow	Lower end of trachea on right side	None recorded
Krausey[5] 1953 ...	38 F	Chest pains	Autopsy	Midway down esophagus	None
Caldwell[6] 1954 ...	54 M	Repeated pneumonia; vomiting	Barium swallow	⅓ way down the esophagus	None
Lansden[7] 1960 ...	63 F	Recurrent pneumonia; choking with food or fluids	Endoscopy	Suprasternal notch	Ligation of fistulous tract
Zack[8] 1967	32 M	Repeated pneumonitis; coughing and choking with liquids	Barium swallow	6 cm above carina	Surgical division and closure
Tenta[9] 1967	16 M	Coughing and choking with fluid intake since birth	Barium swallow	3rd dorsal vertebra	Surgical division and closure
Stephens[10] 1970 ..	15 F	Recurrent choking since infancy	Barium swallow	Level of 2nd rib	Surgical division and closure
Bartelsen[11] 1970 ..	48 M	Recurrent respiratory infections since infancy; coughing with food intake	Barium swallow and Endoscopy	5 or 6 cm above carina	Surgical division and closure

of mucosal sutures of catgut and an outer layer of fine silk. A flap of pleura was placed between the two lines of closure for additional protection.

Except for a transient air leak from the trachea, the postoperative course was completely smooth. The patient's cough rapidly disappeared, he gained weight promptly, and within a few weeks after operation was fully recovered. He remained well thereafter.

Comment

Since the esophagus is not obstructed in tracheoesophageal fistula without atresia, it is possible for most of the food and fluids to pass into the stomach without being sidetracked into the tracheobronchial tree. This probably is what has enabled the few survivors to live to adulthood.

The diagnosis of the H-shaped fistula is made by the actual visualization of the tracheoesophageal connection. This may be difficult because the opening can be small.

The methods employed to demonstrate the fistula include bronchograms, endoscopy, and barium studies of the esophagus. Barium swallow with the patient prone may be successful when other means fail. In any suspected case, therefore, it is important to use this method if other procedures have not demonstrated the fistula.

Correct diagnosis and surgical treatment is of the utmost importance because the lesion is curable.

Summary

Rarely a patient with congenital side-to-side tracheoesophageal fistula will survive to adult life. Reports of 11 such cases were found in the literature. The defect can be an obscure cause of chronic lung disease until diagnosed and surgically corrected, as it was in the case herein reported. Barium swallow with the patient prone may demonstrate the fistula when other methods have failed.

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Refer to: Glick ID, Goldfield MD, Kovnat PJ: Recognition and management of psychosis associated with hemodialysis. Calif Med 119:56-59, Nov 1973

Recognition and Management of Psychosis Associated with Hemodialysis

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ACUTE PSYCHOTIC REACTIONS occurring in association with hemodialysis for chronic renal failure necessitate intensive and immediate medical and psychiatric intervention. Previous reports have focused on the more insidious psychological consequences of this procedure for both patients and staff[1-5] but have largely neglected acute psychotic reactions—particularly with respect to diagnosis and management. A recent case, in which such problems arose, is reported here.

Report of a Case

In December 1970, a 48-year-old farmer collapsed and was brought to Moffitt Hospital, San Francisco, where he was found to be in renal failure. He had been known to have hypertension and polycystic kidneys since age 41 and had been under treatment for hypertension since that time. After initial evaluation, peritoneal dialysis and then hemodialysis, he returned home on 31 December 1970, and thereafter was dialyzed as an outpatient.

There had been no previous overt psychiatric problems, although the patient had been mildly fearful of doctors and hospitals in general.

After he left the hospital, he had dialysis three times, for six hours each time, via an arteriovenous fistula with a Travenol RSP Kidney, without apparent adverse reaction. While at home, he ruminated about being unable to work and was fearful of dying. However, he felt unable to express these feelings, and he become isolated and withdrawn from his family.

Twenty-four hours after completion of the third dialysis, there was an abrupt change in his behavior. He suddenly began crying, then became euphoric and expressed unrealistic optimism that the insurance company would buy him a dialysis machine. He threw himself on the floor, was confused, and said that it was nighttime (at 3 p.m.).

He was immediately taken by ambulance to the private dialysis unit, still agitated, disoriented as to time, and expressing fear that he might "throw himself out of the window." At this time, his serum sodium concentration was 138 mEq, potassium 4.2 mEq, chloride 98 mEq, and bicarbonate 26 mEq per liter. The serum calcium concentration was 8.5 mg, phosphorous 3.6 mg, blood urea nitrogen 50 mg and creatinine 8 mg per 100 ml. Dialysis was carried out that evening and he was twice given 50 mg of chlorpromazine intramuscularly, once before and once during the procedure. The psychiatric symptoms gradually improved during dialysis.

The patient was then transferred to University Hospital, where he was found to be free of hallucinations and oriented as to time, place, and person, but with a decrease in recent memory. He was fearful that the staff would "harm him." On the second hospital day, these symptoms had lessened. During dialysis on the third hospital day, he started to run from his bed to the elevator, but was restrained. As he came to, he imagined that a dish of ice cream had actually appeared before him and that he was eating it. Only when he tried to taste it did he realize there was none. Later that day, he had an episode when he was afraid the staff were going to kill him with a knife.

Careful evaluation of metabolic phenomena, including serum levels of urea, calcium, magnesium, electrolytes and glucose, failed to suggest any cause for an acute brain syndrome. No dialysis bath toxins or concentration errors or disequilibrium syndrome could be identified, and there was no abrupt change of blood pressure or weight to suggest a mechanism for his acute brain syn-

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From the Clinical Research Ward, Langley Porter Neuropsychiatric Institute, University of California, San Francisco.

This paper was presented in part at the American Psychiatric Association meeting in May 1972.

Submitted November 16, 1972.

Work partially completed during the tenure of a Career Teacher Award to Dr. Glick from the U.S. Public Health Service.

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drome. Because of the patient's suicidal ideation, confusion, agitation, paranoid delusions, and the uncertainty as to diagnosis, he was transferred on the fourth day to the Langley Porter Neuropsychiatric Institute.

On admission, he was confused and suspicious. There was no thought disorder. His affect was inappropriately complacent, but not flat. He was disoriented as to time but not to place. Sensorium was clouded; for example, he could not do simple calculations. He was concrete in proverb interpretations. Judgment was poor and insight was lacking.

An electroencephalogram the day after admission revealed an asymmetrical slow record with diffuse dysrhythmia.

He was diagnosed as having both (1) a psychosis associated with metabolic disorder secondary to hemodialysis[6] (although no metabolic abnormality was evident on the laboratory tests done, the presence of confusion, disorientation and memory loss and the abnormal EEG suggested an organic brain syndrome) and (2) an adjustment reaction of adult life (diagnosed on the basis of the fact that this was a transient disorder in a person without apparent underlying mental disorder, and represented an acute reaction to dialysis).[6]

Treatment was directed at immediate reorientation of the patient. He was placed in a well-lighted room beside a locked window, and a calendar, a clock, and a television set were supplied. A nurse was assigned to him for each eight-hour shift, each nurse keeping the same shift each day. Each nurse would frequently state the date, the time of day and the place. The patient's wife was encouraged to spend many hours with him each day and evening in an attempt to produce a familiar environment and to reduce his paranoid delusions and resultant anxiety. A psychiatrist visited him several times a day for short periods. Subsequently, dialysis was performed thrice weekly without exacerbation of his organic state. His symptoms cleared within three days.

Following this, the patient was treated with individual and family psychotherapy. Some of the stresses in his and the family's life were discussed. In spite of the continuation of massive denial at times, he appeared to benefit from psychotherapy and requested that if possible his therapist see him from time to time after discharge from the hospital. No psychoactive medications were used. He was discharged after fourteen days.

A 30-month follow-up revealed no subsequent psychotic episodes. The patient has been followed by his nephrologist and in group therapy with other chronic dialysis patients.

Discussion

It is likely that increasing use of hemodialysis will be accompanied by an increasing number of psychotic reactions. Previous reports of such cases have been nonsystematic and incomplete (see Table 1). The role of psychiatric evaluation and therapy in preventing and managing such episodes has not been clear.

Table 1 suggests that symptoms will vary from a classic organic brain syndrome with symptoms such as confusion, disorientation, and memory loss, to syndromes resembling an acute schizophrenic episode (but usually without a classic "thought disorder" such as ambivalence, autism or the like), or psychotic depression with symptoms such as depression or ideas of reference. These signs and symptoms can occur in the absence of biochemical abnormalities.

The pathogenesis is not known. We would emphasize that these reactions appear related to the simultaneous occurrence of both rapid metabolic changes[7-10] and real environmental stresses[5,11-13]—for example, dependence on "the machine" in order to live. The crucial factor may be the *rate* at which the uremia develops, the swift increase producing a rapid shift of an unknown toxin or shift in water-salt balance.[15] It is possible, then, that the rapid clearing of the mental status is part of the natural history of the syndrome.

Although clouding of the sensorium may occur in association with other situations—namely, chronic uremia or in the diuretic phase of acute renal failure—it is our impression that non-delirium-related functional signs and symptoms are a more prominent part of the clinical picture in association with dialysis than in the other two situations.

Because the pathogenesis is unknown, treatment is empirical. Nevertheless, in view of the life-threatening nature of the symptoms, recognition of this syndrome and vigorous collaborative treatment by both internists and psychiatrists is mandatory. At the earliest manifestation of confusion, disorientation, memory loss, or bizarre thoughts and behavior, immediate investigation should be made to determine, if possible, the etiologic factors involved. First, metabolic alterations should be dealt with by use of dialysis and other measures appropriate to the individual case. If delusions, illusions, hallucinations or other signs of deficit in reality testing appear, phenothiazines may be given—hourly if necessary. The patient's blood pressure should be monitored frequently to detect any untoward hypotensive effects of the phenothiazines. Sedative-hypnotic medication can be utilized briefly to quell severe agitation and restlessness. Judicious use of properly applied arm and leg restraint while waiting for the psychosis to clear can be lifesaving.

Emotional support is critical. Nurses should be instructed to familiarize the patient with the day, the time, the place and the situation, as well as to assist him with the basic necessities. Continued and frequent observation by the psychiatrist is necessary because of the rapidly changing mental status. Psychiatric hospitalization will often be indicated to prevent self-destructive behavior and to deal with delusional behavior, agitation, and restlessness. Later on, a psychiatric setting is optimum to help the patient and family cope with the stresses of chronic dialysis.

Summary

A case of a 48-year-old man presenting with acute psychotic symptoms during outpatient hemodialysis for chronic renal failure, and who became suicidal and homicidal, in the absence of detectable metabolic abnormalities, is described because the diagnosis was missed. A review of the literature revealed only one other well documented case. Symptoms varied from those associated with a classic brain syndrome to those resembling an acute schizophrenic episode.

Collaborative medical and psychiatric management is recommended, with stress on immediate measures to prevent suicidal and homicidal behavior and later on interventions to prevent recurrences of psychosis. In this and the previously reported case, the symptoms gradually cleared from three to ten days after onset and there was no recurrence in a 12-month follow-up.

TABLE 1.—*Data from Previous Reports of Psychosis or Psychotic Symptoms in Association with Hemodialysis*

Authors	*Year*	*N*	*Premorbid Personality*	*Symptoms*	*Psychiatric Diagnosis*	*Management*	*Outcome*
Locke, Merrill, Tyler[14] ...	1961	6	One patient had a 1-year history of "personality disorder"	1. Confusion; 2. Disorientation; 3. Mood changes; 4. Paranoid	Not stated	Not stated	"Mental status recovery was in reverse order to loss"
*Tyler[15] ..	1965	6	"Unstable personalities beforehand"	1. Confusion; 2. "States like delirium tremens"; 3. "Schizoid delusions"	"Psychotic state"	Not stated	"Symptoms often lasted as long as 12 to 17 days, usually gradually abating and becoming less pronounced after 7 to 10 days"
†Brown, Maher, Lapierre, et al[11] ...	1962	1	"Previous personality disorder"	1. Paranoid	"Paranoid psychosis"	Not stated, but psychosis persisted despite dialysis and it was discontinued	Patient died semicomatose still with psychosis
†Gonzalez, Pabico, Brown, et al[16] ...	1963	3	Not stated	1. Depression; 2. Paranoid	1. "Paranoid psychosis" in one patient; 2. "Severe depressive reaction" in two	Not stated	Not stated
†Shea, Bogdan, Freeman, et al[1] ...	1965	3	Not stated	1. "Schizophrenic-like episodes" in two patients; 2. "Psychotic-depressive reaction" in 1 patient	Not stated	1. Regular team conference; 2. Group and individual psychotherapy	Not stated
Cooper[12] .	1967	1	"Apparently normal"	1. Hypomanic-labile, pressured, flight of ideas, grandiose delusions; 2. No delirium	"Acute hypomanic psychosis"	Chlorpromazine—150 mg/day initially, then 200 mg for 10 days, then 75 O.D., all P.O.	Gradual amelioration of symptoms over 10 days; well on 6-month follow-up
Glick, Goldfield,	1971	1	Schizoid	1. Confusion; 2. Disorientation; 3. Memory loss; 4. Labile; 5. Paranoid	Psychosis associated with metabolic disorder and adjustment reaction of adult life	1. Environmental manipulation; 2. Chlorpromazine 50 mg I.M.; 3. Individual, group and family therapy	Symptoms cleared 72 hrs. after onset; no recurrence on 30-month follow-up; dialysis continued to present

*Merrill's group †Schreiner's group

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Lymphangiography in Diagnosis of Fever of Unknown Origin

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WHEN FEVER PERSISTS and the cause remains unknown despite extensive evaluation, surgical exploration of the abdomen is frequently recommended for diagnosis.[1-4] This procedure has considerable merit because intra-abdominal processes that may cause fever—for example, lymphomas of the retroperitoneal space[3,5] are frequently occult. However, there are many extra-abdominal causes for persistent fevers that are quite important (among them tuberculosis, subacute bacterial endocarditis, polyarteritis) and these may also elude early diagnosis. As a result, the decision to operate and the timing of the operation are clinical judgments which are exceedingly difficult. We recently performed lymphangiography as part of the preoperative evaluation of a patient with a persistent fever. Because such use of lymphangiography has been reported infrequently,[3,6] we report our experience to emphasize the value of this procedure in the early diagnosis of fever of unknown origin.

Report of a Case

A 55-year-old male agronomist was referred to the Sacramento Medical Center in April 1972 for evaluation of fever and fatigue of two months' duration. With the exception of these symptoms the history was unremarkable. On physical examination the patient was observed to be chronically ill-appearing, the temperature was 39.8°C (103.6°F), blood pressure 130/80 mm of mercury and pulse rate 108 per minute. A non-pruritic maculopapular rash was present over the chest and abdomen. There was no palpable enlargement of lymph nodes, liver or spleen.

Laboratory studies showed a hematocrit of 35, a leukocyte count of 5,100 per cu mm with 49 percent polymorphonuclear neutrophils, 32 percent lymphocytes, 18 percent monocytes, and 1 percent eosinophiles. The platelet count was 155,000 per cu mm. The erythrocyte sedimentation rate was 53 mm in one hour (Wintrobe). Results of urine and cerebrospinal fluid examinations were normal. Blood chemistry determinations, including glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase, lactic dehydrogenase, bilirubin, albumin, globulin, urea nitrogen, uric acid and haptoglobin were within normal limits. Antinuclear antibody, rheumatoid factor tests, direct and indirect Coombs tests, the VDRL test and serum protein electrophoresis were negative. The feces was guaiac-negative. An electrocardiogram was normal.

No abnormalities were noted in roentgenological examinations of the chest, skull, esophagus, stomach, subphrenic space, small intestine, large intestine, gall bladder, and common bile duct. An intravenous pyelogram revealed a horseshoe kidney. A radionuclide scan of the liver was normal. Skin tests with coccidioidin, intermediate strength tuberculin, histoplasmin, and mumps antigen were nonreactive. Agglutinins for typhoid O, typhoid

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Submitted April 3, 1973.

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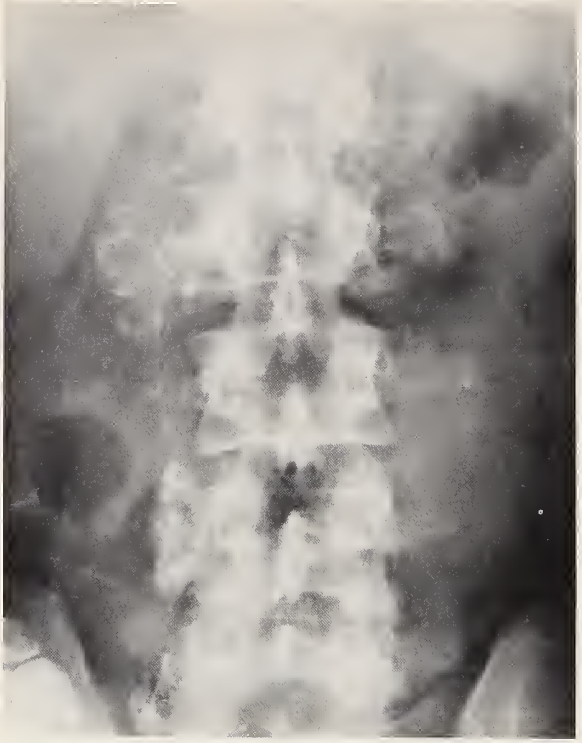

Figure 1.—Lymphangiogram showing enlarged para-aortic lymph nodes which are foamy in appearance and contain filling defects.

H, paratyphoid A, paratyphoid B, Pasteurella tularensis and Brucella abortus were negative, as were blood smears for malaria, and examination of feces for ova and parasites. Cultures of blood, and urine were sterile. A biopsy of bone marrow was interpreted as showing granulocytic hyperplasia. A liver biopsy (Menghini) showed no abnormality. Chronic inflammation was noted in a biopsy specimen from the maculopapular skin rash. Cultures of the biopsy material did not grow either nonacid-fast or acid-fast bacteria, or fungi.

Lymphangiography on the tenth hospital day disclosed enlarged para-aortic abdominal lymph nodes which were compatible in appearance with malignant lymphoma (Figure 1). Abdominal laparotomy was carried out three days later. Biopsy specimens from the enlarged lymph nodes which lay beneath the horseshoe kidney were diagnostic of Hodgkin's disease. The tumor was also present in a liver biopsy specimen and in the excised spleen.

Postoperatively, the patient continued to have high spiking fevers. He was treated with methyl prednisolone, cycloposphamide, vincristine, and procarbazine. After transient improvement, leukopenia developed with fewer than 300 white blood cells per cu mm—all lymphocytes. Despite treatment with gentamicin (1.7 mg per kg of body weight every 8 hours, intravenously) and carbenicillin (400 mg per kg of body weight per day by continuous intravenous infusion) the patient died of pneumonia. Pseudomonas aeruginosa and Escherichia coli grew on cultures of the fluid.

The significant findings at autopsy were Hodgkin's disease involving the bone marrow, liver, and lymph nodes (pelvic, abdominal thoracic, cervical). There was agranulocytosis of the bone marrow and five-lobe, hemorrhagic bacterial pneumonia caused by P. aeruginosa and E. coli (susceptible, by *in vitro* testing, to gentamicin and carbenicillin).

Discussion

This case illustrates the value of lymphangiography in evaluating fever of occult origin. The roentgenographic features were sufficiently distinctive to predict that a lymphoma involving the para-aortic lymph nodes would be found at laparotomy. However, additional experience is needed to assess the reliability of the procedure. It is likely that falsely positive results occur due to nonspecific lymphadenitis[8] or to other neoplasms.[9] Of equal concern is the possibility of falsely negative results—a possibility that is real but apparently small with lymphoma.[7,8] Although these potential sources for crror exist, the high degree of correlation between positive histologic and radiographic findings—more than 80 percent—suggests that the technique will be diagnostically reliable.

The major hazard from lymphangiography is the rare occurrence of an oil embolus.[10,11] Absolute or relative contraindications are few; they include parenchymal pulmonary disease, a patent foramen ovale and allergy to iodine.[8]

Lymphangiography is also of value in localizing the site of lymph node involvement. In our patient, the lymphangiogram located grossly diseased nodes beneath the horseshoe kidney enabling the surgeon to select an appropriate site for biopsy.

Summary

Lymphangiography of the retroperitoneal lymphatic system was performed early in the evaluation of a patient with a persistent fever of unknown cause. The roentgenograms demonstrated enlarged para-aortic lymph nodes which were compatible in appearance with a malignant lymphoma. Abdomi-

nal laparotomy confirmed the preoperative diagnosis.

Retroperitoneal lymphangiography is recommended as a useful procedure in the preoperative evaluation of patients with persistent fevers of unknown cause.

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LETTERS *to the Editor*

Hazards of Sound-Alike, Look-Alike Drug Names

To the Editor: I have compiled a listing of drugs whose names look alike or sound alike. When a pharmacist takes a prescription over the telephone or attempts to decipher a physician's handwriting, a drug product not intended by the prescriber might be dispensed. Such an error might be the result of a sound-alike or look-alike drug.

I have appended a partial list of such drugs with striking similarities. Physicians are urged to exercise great care when writing or telephoning prescriptions.

Benjamin Teplitsky, RPH
Brooklyn

Drugs Whose Names Look Alike or Sound Alike

1.	Aerolone	Aralen	Arlidin
2.	Ananase	Orinase	Tolinase
3.	Anavar	Anavac	Antepar
4.	Arfonad	Afrin	Aspirin
5.	Asminyl	Asmolin	Esimil
6.	Benadryl	Benylin	Bentyl
7.	Butisol	Butibel	Butabell
8.	Capla	Keflin	Keflex
9.	Chlorambucil	Chloromycetin	Chlor-Trimeton
10.	Coramine	Calamine	Calomel
11.	Cordex	Cordran	Codeine
12.	Demerol	Dicumarol	Deprol
13.	Digoxin	Digitoxin	Desoxyn
14.	Dilantin	Phelantin	Delalutin
15.	Disipal	Disophrol	Stilphostrol
16.	Donnatal	Dianabol	Donnagel
17.	Dopar	Dopram	Dorana
18.	Doriden	Loridine	Doxidan
19.	Elavil	Aldoril	Mellaril
20.	Empirin	Empiral	Emprazil
21.	Enduron	Imuran	Eutron
22.	Esimil	Estinyl	Ismelin
23.	Estomul	Ilomel	Isomel
24.	Ethamide	Ethionamide	Ethinamate
25.	Feosol	Feostat	Festal
26.	Haldrone	Halodrin	Haldol
27.	Harmonyl	Hormonin	Homapin
28.	Isordil	Isuprel	Isomel
29.	Kaomin	Kao-Con	Kaon
30.	Kelex	Keflex	Keflin
31.	Maalox	Maolate	Marax
32.	Mebaral	Mellaril	Medrol
33.	Meprobamate	Meperidine	Mepergan
34.	Mesantoin	Mestinon	Metatensin
35.	Modane	Matulane	Mudrane
36.	Ornex	Orinase	Ornade
37.	Pantopon	Protopam	Parafon
38.	Pathocil	Pathilon	Pitocin
39.	Peritrate	Lotusate	Pentryate
40.	Persantine	Persistin	Trasentine
41.	Sansert	Cenasert	Singoserp
42.	Sterazolidin	Butazolidin	Stelazine
43.	Temaril	Demerol	Tepanil
44.	Thyrar	Thyrolar	Tryptar
45.	Urised	Urestrin	Uracel
46.	Urithol	Uritral	Uritone
47.	Valadol	Vallestril	Vistaril
48.	Valmid	Velban	Valpin
49.	Vontrol	Vastran	Vosol
50.	Zactirin	Saccharin	Zentron

Professional Competence

To the Editor: The editorial in California Medicine [119:71-72, Aug 1973] entitled "Some Problems in Assuring the Professional Competence of Physicians" is of interest to the American Society of Internal Medicine because it clearly identifies the elements in this arena that have concerned us so much.

The ASIM has deplored the current trend for State medical associations to use evidence of continuing medical education efforts as a requirement for continued Association membership, or, worse, for relicensure.

The popularity of such moves is apparently based on the ease with which such evidence can be gathered, not on any conviction that attendance at educational functions really measures clinical competence.

We in ASIM believe that a preferable method is to assess actual performance. The CMA's "practice audit" is an innovative example of this concept. We believe that determined efforts on the part of the profession—started now with PSRO as a stimulus—can perfect existing techniques so as to truly assess medical care performance. Anything less will fail to give the public the honest assurance of continued competence it demands.

William Campbell Felch, MD
President, ASIM
Rye, N.Y.

A Message from the President

FELLOW PHYSICIAN:

California physicians have led the nation in most areas of medicine, particularly in the field of continuing medical education. In response to the public's increasing concern for and interest in high-quality health care and in answer to the Legislature's cry that physicians should be subject to mandatory licensure controls, the California Medical Association inaugurated a voluntary program for the reporting of continuing medical education. CMA's Committee on Continuing Medical Education hopes that the program also acts as an impetus to physicians who might not otherwise pursue their personal educational needs.

More than 3,000,000 hours of continuing medical education efforts have been officially documented by 10,000 California physicians. This program meets all the continuing education requirements of the AMA and the mandatory requirements of the California Academy of Family Physicians and the California Society of Anesthesiologists. You need only fill out one form. (Forms were mailed to all California physicians during September.) The information is recorded, computerized and provided to your hospital, specialty society, or AMA, upon your request. A certificate suitable for framing is issued upon completion of 200 hours in a three-year period.

Each of us spends untold hours reading journals, attending rounds, listening to medical lecture tapes (such as Audio-Digest), going to specialty meetings, attending CMA scientific sessions, and the like. Our patients and our lawmakers have a right to know that their physicians are well-trained and up-to-date on medical advances. We have an obligation not only to keep ourselves informed but also to assure others of the competence within our profession. By accepting this responsibility voluntarily, we hope to convince society that there is no need for mandatory periodic reexamination and relicensure, or for undue controls placed on California physicians by "outside" agencies.

I hope you will take a few minutes to record your activities and support our efforts in continuing medical education.

THOMAS ELMENDORF, MD
President
California Medical Association

Refer to: Rosenberg SH: Informed consent—A reappraisal of patients' reactions (Medical Jurisprudence). Calif Med 119:64-68, Nov 1973

Informed Consent

A Reappraisal of Patients' Reactions

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In response to the November 1972 ruling of the California Supreme Court requiring complete, detailed disclosure of risks for procedures and treatments, a survey was made of the reactions of one hundred patients to this decision. A fictional man was described with a clinical diagnosis of brain tumor, and then the procedure for cerebral angiography and all of that procedure's potential complications were described. The majority of the patients surveyed responded that this complete disclosure of risks helped them in making an intelligent decision about giving consent for the procedure. However, 50 percent of these patients would have withheld consent for the procedure on learning of the complications. Although physicians would have reacted differently, it is certainly the patients' right to make the choices they did.

THE ISSUE OF INFORMED CONSENT has been a source of heated and often acrimonious discussions by physicians and attorneys. However, aside from a recent study from the Cleveland Clinic, which will be discussed below, patients' views have received little attention. A recent decision by the California Supreme Court has forced the issue to the forefront again.

Physicians' views on the subject tend to be one of the following:

- The patient must be told everything about any complications that might ensue from a procedure or treatment.
- The patient must be told nothing because it is a waste of time. (The rationale for this position is that patient lacks the background to scientifically weigh the advantages and disadvantages of a medical decision.)
- Telling patients about threatening complications will cause undue anxiety which the patient can not handle.
- Detailed recitals of complications will result in patients' withholding of consent for procedures which their physicians feel are necessary.

Proponents of the last three views have argued that litigation over informed consent represents post hoc thinking, and that a complaint about inadequate information would never have been raised had the complication not occurred in the first place. They argue further that the informed consent concept is an expedient means of charging negligence when no negligence has occurred.

Attorneys have argued, on the other hand, and the current wave of consumerism in this country has supported them, that complete disclosure of advantages and disadvantages of any product or service is a basic right. There has been an implication on the part of the legal profession and plaintiffs that the physician who provides "inadequate" information about complications is trying

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to delude the patient. That this is rarely the case is, unfortunately, not generally appreciated outside the medical profession.

Dr. Ralph L. Alfidi provided a study of the patients' viewpoints of this topic.[1] His article reported the experience of the Cleveland Clinic with two separate studies. The first involved a detailed statement of the technique of angiography, followed by careful statements about thrombosis at the arterial puncture site and hematomas in the groin and more general statements about anaphylaxis and the possibility of stroke. The clinic's staff felt that this form was unnecessarily frightening to the patients; hence, a second form was adopted in which the complications were described in more general terms. The form was very favorably received by the patients. Eighty-nine percent of the patients felt that the form provided useful information. In response to this more general second form, 73 percent of the patients polled stated that they did not want more specific information about complications. Only 2 percent refused consent for the procedure on the basis of the complications mentioned on the form.

In November 1972, the California Supreme Court reviewed the issue of informed consent and issued rather sweeping changes in the consent laws as follows:

- With a complicated procedure the patient may choose to have a complete disclosure of complications or may choose to forgo such a disclosure.
- If he elects to have the complete disclosure, then he must be told about every foreseeable complication that is of serious medical consequence or that is potentially fatal.
- The patient no longer needs an expert witness to explain to the jury what the standard disclosure by the medical community would have been in a given case, but rather the jury can decide if the disclosure has been adequate.
- The proof that a patient-plaintiff would have refused a procedure if he had knowledge beforehand of such a complication would also be for the jury to assess. (In other words, the jury would be asked to decide, What would a prudent man do in similar circumstances?) Dr. David Rubsamen, an authority on Medico-legal affairs, concluded in his review of this case[2] that this verdict may well have a profound effect on future informed consent decisions all over the country.

Since we were concerned to see how patients as well as physicians would react to these changes, we began a study of patient responses to full disclosure of complications. As the situation was experimental, we elected not to begin our study with patients who were themselves going to have this procedure done, but rather sampled one hundred people who had no experience with the procedure at all.

Methods

One hundred patients ranging in age from 20 to 70, with an equal distribution of men and women, were given a printed questionnaire to be answered in the physician's office. Before they began their interviews, the patients were told that this was an experimental survey and that its purpose was to better understand patients' views on informed consent.

A fictional 55-year-old man was described whose only medical problems were headaches and left hemiparesis. On the basis of a full clinical examination and a brain scan, a provisional diagnosis of a mass lesion was made. The patients were told that the most definitive way to visualize the location, determine the probability of malignancy and the blood supply of the tumor (if tumor it was) was to obtain a cerebral arteriogram. They were also told that there was a possibility that the lesion was not a tumor, but that all indications were that it was. Also, if this were a tumor, the patient's symptoms would inevitably get worse and progress to a vegetative state and death. On the other hand, the study might demonstrate a potentially resectable lesion. They were then told that they would have to weigh this clinical state against the complications of the procedure. The overall complication rate for Kaiser Foundation Hospitals was given as 1.5 percent with an incidence of permanent neurologic sequelae of 0.5 percent. A detailed statement in lay language of the mechanics and technique of cerebral angiography was then given. Then all possible complications were listed and described in lay language, followed by a place for a yes or no response for each complication. The patients were asked to review the clinical situation of this fictional patient and the details of the procedure involved. They were then to decide, for each complication (putting themselves in this patient's shoes) if having knowledge beforehand of a given complication would cause them to withhold consent for the procedure. The complications as they were stated to the patients are listed in Exhibit 1, followed by the responses to each question. Some general questions were then asked (listed in Exhibit 2) to assess the patients' general reactions to complete disclosure.

All the questionnaires were administered by one physician so that the explanation would be uniform. However, the patients had to answer all the questions by themselves. Any requests for the physician's opinion were denied. This was done to avoid any element of persuasion and also to avoid the variable of the individual physician's personality.

EXHIBIT 1.—*Patients' Attitude Toward Having Cerebral Arteriogram for Diagnosis and Location of Tumor*

Question	*Percent YES**	*Percent NO†*
1. You will have to lie perfectly still on a hard table for several hours during the procedure.	7	93
2. In rare instances, an allergy to the contrast medium might not be anticipated prior to the procedure. Hence, an allergic reaction might occur which would involve chills and welts over the skin. This might progress to shortness of breath. In extremely rare situations, an allergic reaction could be fatal.	14	86
3. In some patients the bleeding that naturally ensues when the artery is punctured may not be stopped totally. Under those circumstances, the blood may ooze out and form a large swelling in the groin called a hematoma. This eventually dissolves, but it can be very painful during the period of resolution which can be several days to a full week.	3	97
4. Some patients may have atherosclerosis in the large artery in the groin. Such patients rarely may form a clot in that artery at the end of the procedure. The presence of such a clot in the artery would make the leg cold and numb and painful. If such a clot develops, it has to be removed by a surgeon. This surgery is almost uniformly successful if done early. However, it is major surgery and it does involve general anesthesia.	7	93
5. The most important complications from arteriograms are due to strokes. A stroke means that a blood vessel in the brain has been blocked; hence, the brain tissue supplied by that blood vessel will become diseased and may be permanently injured. Most of these strokes are short-lived and clear up within one day. The incidence of permanent strokes is about 0.5 percent. Below are listed specific problems which can occur with strokes		
Complications		
(a) The arm on one side of the body might become very weak.	12	88
(b) The leg on one side of the body might become very weak.	13	87
(c) Both the arm and leg on one side of the body might be very weak.	16	84
(d) Sensation might be reduced or lost on one arm.	16	84
(e) Sensation might be reduced or lost on one leg.	19	81
(f) Sensation might be reduced or lost on one arm and leg.	19	81
(g) The ability to speak might be impaired. This might take the form of inability to say the word, inability to think of the word you wish to say, or inability to understand what is said to you.	32	68
(h) Double vision.	25	75
(i) You may be unable to see half or one quarter of your visual field.	26	74
(j) You may have abnormal sensations on your face which would make it feel asleep.	23	77
(k) You may have trouble chewing or swallowing.	23	77
(l) Decrease or loss of vision in one eye.	26	74
(m) In extremely rare situations, as a result of multiple strokes, you could come out of the procedure with decreased consciousness, unable to move or talk. You would have to be watched constantly by nurses and be nourished by vein.	28	72
(n) Rarely, you might die from the procedure.	24	76

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*YES—Knowledge of this would cause me to refuse the procedure.
†NO—I would consent anyway.

EXHIBIT 2.—*Patients' Attitude Toward Detailed Discussion of Procedure and Risks*

	Percent YES	*Percent NO*
1. Do you feel that such a detailed discussion of risks helps you to make an intelligent decision for yourself about the procedure?	73	28
2. Conversely, does it hinder you in making such a decision because of disturbing worry?	27	73
3. Would you have preferred to have only been told about the procedure itself and not the complications?	24	76

Results

The percentages of patients who responded "yes" or "no" to our questions are given in Exhibits 1 and 2.

Our physician colleagues predicted that most patients would respond that a detailed discussion of risks would be of help to them; that it would not create so much disturbing worry as to hinder their thinking; and that they would not have preferred a consent method which only described the procedure and gave them no idea of the complications. As can be seen from the Exhibits, the prediction was born out in most cases. Fifty-four percent of those who disagreed indicated that none of the complications would have prevented them from giving consent for the procedure. That would seem to be a perfectly logical response for someone who in some way disapproved of a technique of complete disclosure. Nevertheless, there were 11 patients who stated that they did not feel that a detailed discussion of risks helped them in making an intelligent decision about having the procedure done, but they still would have withheld consent because of one complication or another. There were 17 who felt that disclosure caused them disturbing worry which hindered their making a decision, but who would have refused consent anyway because of complications. Ten patients who stated that they would have preferred to have only been told about the procedure itself and not the complications would have withheld consent for the procedure when they found out about complications.

Of the 100 patients surveyed, 50 would have withheld consent because of one complication or another. Of these, 30 limited their refusals of consent to knowledge of specific stroke syndromes. The remaining 20 did not so limit themselves.

Discussion

The majority of the patients polled responded as we had predicted. However, it should be noted that the percentages of those who disagreed, though in the minority, were not small. This would support the Supreme Court's contention that a full disclosure is not for everyone.

We were surprised to find that 50 percent of the patients polled would have withheld consent for a very important procedure because of knowledge of complications. This result is in glaring contrast to the result of Dr. Alfidi's study quoted above. The major differences between the two studies were: (1) that our patients were answering in the abstract, and his were actually having the studies themselves, and (2) our study included very specific statements about the conditions of patients who have strokes. It might be argued that if these individual complications were reviewed by an actual patient who knew that his personal physician had endorsed the cerebral arteriogram, he might feel more secure in taking the calculated risk in consenting to it. On the other hand, 60 percent of those who would have refused did so only because of specific, detailed knowledge of stroke syndromes, and the highest rates of refusal were for the most sinister complications. This would strengthen our conclusion that the very detailed description of the clinical picture of strokes had some influence on the high rate of refusals for consent in this study.

The spread of responses among the different types of strokes would indicate that there are some stroke syndromes to which some patients would object and others to which still other patients would object. Hence, it would appear that only a complete list of complications would satisfy everyone's needs. Furthermore, it has been my experience as a neurologist that it is unusual for a patient to have any concept of what the term *stroke* means. Hence, patients must be told more than "You may have a stroke." As might have been anticipated, the largest numbers of negative responses were in connection with the most threatening clinical states—aphasia, blindness, coma, and death. That such clinical states might emerge from the tumor itself did not seem to have swayed the patients' thinking.

Although the question was not asked, many patients volunteered that they found the kind of thinking required in this questionnaire to be very difficult and that they were totally unprepared for decision-making of the kind the study required. Perhaps in a few years when the public is more accustomed to thinking of this type, the results of such a study would be different. In the meantime, perhaps the spreading wave of consumerism will make patients aware of their rights and of their responsibilities for their own decisions.

In conclusion, the results of this study would certainly suggest that the Supreme Court's opinion is in accord with what the majority of our patients desire. The majority of patients felt that a complete, detailed discussion of risks did help them in making an intelligent decision about consenting to a procedure; that they were not hindered in making the decision because of the disturbing worry that ensued; and that they wanted to know about the complications as well as about the procedure. The Supreme Court's ruling also makes it possible for those who do not want a full disclosure of risks to choose accordingly.

We were somewhat upset to find that 50 percent of the patients polled would have withheld consent for this procedure because they knew about complications. It can only be hoped that their refusals would be based on as thorough an *understanding* as possible of the relative prognosis of their disease versus the relative risks of the procedure.

Acknowledging the mitigating factors mentioned above, we are left with the conclusion that when patients are given a complete disclosure of risks, their choices about this procedure would be at variance with what their physicians would have predicted. The Supreme Court decision simply affirms that this variance is the patients' right and it must be respected.

It should be emphasized that the patients who participated in this study had never had neurological problems themselves in the past and were not themselves facing the prospect of angiograms in the future. The purpose of the study was to assess the reactions of patients in general to the experience of a complete disclosure of risks. Now that we have the preliminary experience of this study as background, we hope, in the future, to be able to collect a series of the reactions of actual patients to a complete disclosure of risks.

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Medical-Legal Concepts in the Evaluation of the Injured Workman

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LAWS DESIGNED to compensate a workman for disabilities caused by injuries or illnesses arising from his work are relatively recent. Medieval Common Law depended on the tort concept in which an injured man might seek compensation only if he was hurt by another's negligence.

During the medieval development of trades and trade guilds this principle gave some protection to the working man, since usually skilled workmen in those days hand-made their product and to some extent controlled their working environment. However, with the Industrial Revolution came mills and mines and complex industrial structures where the workman did what he was told to do, and in the manner his employer required. The workman came into greater hazard and at the same time discovered that when he was hurt at work, his only recourse—a trial based on employer negligence—was difficult, costly and often unsuccessful.

As the mills and factories grew larger the employer played a lesser role in work control and consequently was less open to the charge of negligence. Moreover, the legal concept that the employer was relieved of responsibility if a workman's injury was caused by the negligence of a fellow employee prevented recovery in all but a very few instances.

The Industrial Revolution progressed, and economic pressures encouraged faster and more dangerous manufacturing processes. The number of job-related injuries increased and injured workmen were unable to secure compensation during periods of disability. The crippled workman, his widow and his orphan became a great burden upon society, creating a problem that ultimately required a change of public policy.

In England, Dickens wrote trenchantly of the plight of the injured workman. Blake wrote of the "dark satanic mills" of central England. Poets, essayists and clergymen moved the nation's conscience, and were greatly helped by a series of coal mining accidents that killed or crippled many men. Modern laws for workman protection followed.

However, generally protection of American workmen from the dangers of their trade and compensation for those who were hurt lagged behind that of Europe. But in 1909 Alice Hamilton, a public health physician, returned from a meeting with European physicians and denounced the prevalence of lead poisoning in American workmen engaged in the ceramic coating of tubs and toilets. The indignation of this small, determined woman was heeded by legislators, and in state after state

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humanitarian laws were enacted and designed to offer medical care and compensation to workmen injured as the result of their work. The concept of blame or negligence was abandoned as a prerequisite to compensation. In exchange for this concession, the amount the workman could recover was reduced far below his actual loss; he was, moreover, not entitled to a recovery for pain and suffering, but only for the permanent loss of all or a part of his working ability.

The Process in California

In most states separate judicial bodies were created. These were called by various names. In California it is known as the Workmen's Compensation Appeals Board. The trier of fact is known as a referee. His decision can be appealed to Commissioners of the Workmen's Compensation Appeals Board and their decision can be challenged only by a writ of review to the Court of Appeals and to the Supreme Court of the State of California.

Most often, however, it is the referee who makes the final decision and to a great extent he relies on the medical reports from the physicians. From these reports as well as from direct testimony he determines whether the workman's disorder arose out of and occurred in the course of his employment, and, if so, the nature, extent and duration of his disability.

In adjudicating these claims, the Workmen's Compensation Appeals Board has created a nomenclature all its own. An injured employee is entitled to *temporary disability* during the periods of time that he is unable to return to his work. The temporary disability may be *partial* or *total.* Even after he returns to his work, if he has some residual disability, whether partial or total, he may be entitled to further benefits called an award for *permanent disability*. Payment of temporary disability awards stops when the patient's disorder has become *permanent and stationary*—that is, when there is no further prospect for significant improvement or deterioration, subject to the usual fluctuations of any chronic disability. The physician may form an opinion as to what the patient's disability will be in the future.

The permanent disability award is paid on the basis of a rating, or the statement of disability in percentages. The rationale of the permanent disability award is to assist the working man in rehabilitating or retraining himself for a job that he can do with his disability. It is paid over a period of time, the length of time depending on the degree of disability, his age and his occupation. The older a worker is, the greater his rating, since it then would be more difficult for him to rehabilitate himself.

Precision in Use of Terms

Since certain adjectives or qualifying phrases are translatable into disability ratings in terms of percentage, terminology must be exact. Understanding and correctly using the terminology of the Workmen's Compensation Appeals Board is one of the principal problems faced by doctors in writing medical reports that can be comprehended and convey worthwhile information upon which a referee can base his ruling. The compensation laws of this state permit the injured workman's attorney to refer the patient to a physician of his choice for evaluation and a written report. By having the workman sign a Workmen's Compensation Appeals Board form known as a Lien Form, the physician is assured that his fee will be paid by the insurance carrier or employer, provided that fee is reasonable and the examination contributes in some way to the referee's understanding of the workman's illness or injury. In most cases this is true even though the injured workman eventually loses his case. It is a rare case in which the physician does not receive his fee, and this only when he had received so misleading a history from the employee that his report is of little value.

Many physicians are reluctant to write such medical reports for their patients or to have cases referred to them for the purpose of writing medical reports. They fear that they will be called for cross-examination and be subject to harassing questions. Actually there is cross-examination on less than five percent of the medical reports filed. It is only in those cases where the physician is expressing a medical opinion on the basis of records given to him, not on an examination of the patient, that he must testify in person, and even this can often be avoided by a stipulation between the opposing attorneys that a medical report may be submitted in the place of oral testimony.

The opinions of well-qualified physicians are sought for and respected by both adversaries in this humane arena of law. No physician expressing an earnest well-considered opinion need have any reluctance to face cross-examination, since the functioning of this court depends on the medical opinion. The physicians who submit reports to it, and appear before it, serve their community and merit its respect.

A Communicative Language

Once the decision is made to write the report and participate, the greatest challenge is to convert the medical knowledge to terms and meanings that will make sense to the lay adjudicators and assist them in arriving at a decision.

While the language of the report should not be unnecessarily complex, neither should the physician "write down" to the Board. He may assume substantial medical sophistication in the referee and competent attorneys. Ordinary medical terminology is readily understood, and problems of terminology are more likely to lie with the physician's use of "sensitive" Appeals Board adjectives and phrases than with any lack of medical comprehension by the referee or by the attorneys. The inexperienced doctor generally errs on the side of underestimating the medical sophistication of the referee and the lawyers.

One important concept not known to physicians inexperienced in this field is that a workman may have subjective permanent disability with or without concurrent objective findings. The Workmen's Compensation Appeals Board has created certain definitions to help the doctor convert such subjective disabilities into language that the permanent disability rater and the referee can understand in terms of numerical value. The following recommendations and definitions have been adopted and are embodied in Section 9727 of the Rules and Regulations of the Administrative Director, Division of Industrial Accidents.

Subjective disability should be identified by:

1. A description of the activity which produces the disability.
2. The duration of the disability.
3. The activities which are precluded and those which can be performed with the disability.
4. The means necessary for relief.

The terms below are presumed to mean the following:

1. A *severe* pain would preclude the activity precipitating the pain.
2. A *moderate* pain could be tolerated, but would cause marked handicap in the performance of the activity precipitating the pain.
3. A *slight* pain could be tolerated, but would cause some handicap in the performance of the activity precipitating the pain.
4. A *minimal* (mild) pain would constitute an annoyance but causing no handicap in the performance of the particular activity, would be considered as nonratable permanent disability.

These terms have been further modified by usage to interpolate between the above plateaus or levels of subjective complaints. This can refer either to degree or duration of subjective complaints. An example of a description that would have the lowest possible ratable disability would be based upon terms such as *intermittent,* which would apply to duration, and *minimal to slight* pain, which would apply to degree of pain in the area of the body affected, such as the back. Other descriptions utilized in describing degree are *slightly less than slight, slightly more than slight, between slight and moderate, slightly less than moderate,* and *slightly more than moderate.* There is also modification by work limitation such as *between moderate and light work, light to semi-sedentary work,* and *sedentary,* with the further requirement that the employee be precluded from emotional stress—a requirement that might be applicable in the case of, say, heart disability. In addition to describing the duration of the subjective complaint as intermittent, it can also be described as constant or brought about by some specific activity.

Guidelines for Work Capacity

Disabilities are most often both subjective and objective; and in certain fields, most especially in dealing with work-aggravated heart diseases or with lung disease disability, the requirements may occasionally be entirely prophylactic, that is, imposed on the workman to avoid further injury.

In cases of disability due to lung or heart disease, abdominal weakness and spinal disabilities, there are Guidelines for Work Capacity, which are now part of the Schedule for Rating Permanent Disabilities. This amendment applies to injuries occurring on or after January 1, 1970. The guidelines are:

(a) *Disability precluding very heavy lifting*—contemplates the individual has lost approximately one quarter of his preinjury capacity for lifting. (A statement "inability to lift 50 pounds" is not meaningful. The total lifting effort, including weight, distance, endurance, frequency, body position and similar factors should be considered with reference to the particular individual.)

(b) *Disability precluding very heavy work*—contemplates the individual has lost approximately one-quarter of his preinjury capacity for performing such activities as bending, stooping, lifting, pushing, pulling and climbing or other activities involving comparable physical effort.

(c) *Disability precluding heavy lifting*—contemplates the individual has lost approximately half of his preinjury capacity for lifting. (See statement regarding lifting under (a) above.)

(d) *Disability precluding heavy lifting, repeated bending and stooping*—contemplates the individual has lost approximately half of his preinjury capacity for lifting, bending and stooping.

(e) *Disability precluding heavy work*—contemplates the individual has lost approximately one-half of his preinjury capacity for performing such activities as bending, stooping, lifting, pushing, pulling, and climbing or other activities involving comparable physical effort.

(f) *Disability resulting in limitation to light work*—contemplates the individual can do work in a standing or walking position, with a minimum of demands for physical effort.

(g) *Disability resulting in limitation to semi-sedentary work*—contemplates the individual can do work approximately one-half the time in a sitting position, and approximately one-half the time in a standing or walking position, with a minimum of demands for physical effort whether standing, walking or sitting.

(h) *Disability resulting in limitation to sedentary work*—contemplates the individual can do work predominantly in a sitting position at a bench, desk or table with a minimum of demands for physical effort and with some degree of walking or standing being permitted.

The Factor of Preexisting Condition

Physicians are often troubled when they are called upon to express an opinion as to whether work has aggravated a preexisting nonindustrial disorder. While this may happen with preexisting arthritis, or preexisting intervertebral disc disease, perhaps the most troublesome problem of this kind has to do with the precipitation of a myocardial infarct in a patient with preexisting severe arteriosclerosis.

If a man with severe coronary artery disease runs across a parking lot at work, before he reaches the other side he might die of a sudden fatal arrhythmia precipitated by the effort. In considering this example, the natural tendency for a physician is to reason that, since a relatively small effort brought on the death, the effort is not important or determinative but instead the underlying disease far outweighs the terminal act and is therefore determinative. This concept is likely to be valid where the emphasis is on medical treatment. However, if this man would not have died at the actual time he did if he had not run at work, this death would be regarded as occupational in the arena of the Appeals Board hearing rooms.

Reasoning of this type is reflected in our judicial proceedings and by the decisions of the Appeals Board over the years. The problem in this example concerns itself not with the genesis of the arteriosclerosis, since there is no reason to believe in this patient that the arteriosclerosis was occupational. The question posed by claims of this type is whether death was hastened by reason of physical exertion in a man with severe preexisting coronary disease.

This is a relatively clear-cut example of the usual type of cardiac claim, and physicians often find themselves uneasy with legal reasoning of this kind. Their own education leads them to conclude that if the workman with severe coronary arteriosclerosis did not have an attack at one particular moment, he would likely have had it an hour later when he ate his lunch, or a day later when he climbed stairs, or a week later for no external reason at all. Consequently, the death is frequently regarded by such physicians only as a result of the underlying arteriosclerosis, and no weight is to be given to the industrial precipitating factor of his running. Reasoning of this type, while medically attractive, goes counter to several legal precedents.

The Supreme Court of the State of California has held in a case of a claimant who had cancer that even though it was generally agreed by all the reporting physicians that the cancer in itself, without further superimposed trauma, would have caused the patient's death predictably and soon, where this man additionally was so injured in his work that this injury brought the day of his death a little closer, his death was entirely compensable. The Supreme Court suggested in this landmark decision that the true touchstone question as to whether or not death is occupational will depend on the answer to the question: If all occupational factors are withdrawn, would the workman have died at the time he did?

Consequently, in evaluating the case given as example, the proper question for the physician is to ask himself: Would this man have died at the exact time he did if he had not run at his job? If the physician believes that the patient would have died at this same time, then he should make no assignment of responsibility to the patient's work. On the other hand, if the physician believes he died sooner because of the running, then the death is to be considered wholly occupational.

Industrial and Nonindustrial

There is no apportionment or division between occupational and nonindustrial factors in a death claim. By precedent, even if occupational factors play only a small but real part in a workman's death, the occupational factors are to be considered entirely causative. The reasoning behind this judicial opinion is that, if a factor is partially causative of death, even to a small degree, it must also be determinative of the time of death as well. Anything that contributes to death must result in that death's being brought on sooner than it would otherwise. Since adjudication is being made on one death alone, the actual death, and it is not made on the basis of a theoretical death occurring at some future time, all causative or accelerating factors participating in any degree in the actual death are also causative of that death.

In the living workman, on the other hand, occasionally the disability may have both industrial and nonindustrial factors. Then the physician is asked to suggest an apportionment in which he indicates how much of the disability is industrial and therefore compensable and how much is nonindustrial and therefore noncompensable. There is a firm rule governing apportionment. Apportionment must be based only on disability. It may not be based on preexisting pathological changes alone.

Consider the implications of the following case: A workman is diabetic, and has arteriosclerotic disease with advanced vascular insufficiency of both lower extremities. However, he has no working disability, and is able to do all of his work. On a day at work a plank collapsed under his feet and a sliver of wood was driven into one toe. Later the small laceration became infected. In spite of treatment, gangrene developed and finally the patient lost his entire leg below the knee.

The physician knows that the diabetes and the arteriosclerosis are by far weightier than the splinter and the laceration. He is aware that if the patient did not get the small injury that started off the trouble, infection might have developed in a corn or a blister a few weeks later that would cost him his leg. Likely in time, sooner or later, the gangrene would have started by itself, without injury. However, legal reasoning is based on legal precedent, and by such reasoning one must decide the actual injury as it happened. The patient's loss of the leg at the actual time it was lost was in part caused by the splinter that pierced his toe at work on the day of his injury. If the single occupational factor of the small laceration were withdrawn, the workman would not have lost his leg at the time he did. Therefore the actual loss of the leg is to be wholly ascribed to the industrial injury, and no apportionment should be made.

Legal precedent has therefore established that apportionment must be made on the basis of disability, and not on the basis of pathology. The physician who evaluates an injured or ill workman must hold this particular concept before him at all times. While he is called upon to present a medical opinion, this opinion must follow the established rules of legal precedent. He should not substitute for the Workmen's Compensation Law his own principles of apportionment. If he does, his opinion may be disregarded in full or in part, the referee then relying on only portions of the physician's report or on the reports of other physicians. Worse yet, if the structure of opinion is not fully explained, it may lead the referee to an unfair decision.

There are numerous circumstances in which apportionment is necessary. A workman may have chronic back disease with a working disability. If he industrially injures his back further, apportionment will have to be determined between the preexisting nonindustrial disability and the occupational injury. A workman may have a heart attack at home, not considered to be industrial in any part. However, if the attack goes unrecognized and he does hard physical work for two weeks before he is admitted to a hospital, the physician will then have the burden of suggesting how much disability is due to the attack alone and is therefore nonindustrial, and how much is due to aggravation by working during an acute infarct and is therefore industrial.

Apportionment is probably more of a legal discipline than a medical discipline, and the physician may be wise in difficult choices to set out only the medical facts that would underlie apportionment, allowing the referee to apply the relevant legal rules to these facts and determine the amount of apportionment himself.

The problem of apportionment may be involved in a situation not envisioned by the average medical practitioner. If a previously disabled employee incurs a subsequent industrial injury, and the industrial and preexisting factors of disability combined rate 70 percent or more, the employee may be entitled to additional benefits from the Subsequent Injuries Fund. The primary purpose of this fund was to encourage employers to hire the handicapped.

An example of how this law operates: An employee has lost the sight of one eye, and subsequently he receives an industrial injury which causes the loss of the sight of the other eye. He would be then 100 percent disabled. The employer, however, is only liable for the loss of one eye, which rates but 25 percent. The state pays the other 75 percent and the life pension which is assessed on a permanent disability rating of over 70 percent. If there is a preexisting disability to a portion of a limb or an eye and the industrial injury occurs to the opposite member, a relatively minor industrial injury of 5 percent or more may qualify a person for these benefits. If a contralateral member such as an eye or limb is not involved, the industrial injury must alone rate 35 percent.

It can easily be seen, for example, where there is a preexisting disability to the back and a subsequent industrial injury to the same area of the body, the sum of which produces an overall disability of over 70 percent, how the physician determines the apportionment may be very material as to whether an injured employee receives a relatively small financial recovery or an award granting a life pension.

An intriguing area in which legal precedent and legislative code preempts medical opinion relates to the presumption of industrial causation of heart disease in firemen or policemen. According to Section 3212 et al of the Labor Code, coronary artery disease and most forms of heart disease occurring in firemen or policemen is presumed to be occupational. The burden of proof has been shifted, and a policeman or fireman in whom heart disease has developed starts out with the presumption that his work has caused his heart disease. It is then up to the defendant carrier or employer to prove that it has not—a chore that is often quite difficult. Some physicians feel that the prolonged stress and strain of the type faced by firemen and policemen can aggravate or accelerate arteriosclerosis; others do not. Some physicians feel that the clear occupational exposure of firemen to repeated inhalation of carbon monoxide may accelerate arteriosclerosis; others do not. However, the State Supreme Court in another important decision recently made it clear that the Workmen's Compensation Appeals Board was to put aside the opinion of physicians who believe that work cannot contribute to or aggravate arteriosclerotic heart disease in such claimants. It is the physician's prerogative to form any opinions he considers probable. However, if this opinion is built on reasoning contrary to this legal precedent, the referee likely will disregard all or a portion of his opinion.

Open and full description of the basis for the physician's opinion is important in reports intended for submission to the Appeals Board. A physician should expose his reasoning to the examination of the referee. For example in the case of a policeman who has had a heart attack, if the examining physician writes merely that he does not feel that the patient's work in any way contributed to the patient's heart disease, the referee may decide that what the physician has concluded is that this particular policeman's work was not stressful enough to affect his heart, and therefore that the presumption is rebutted. However, if what this physician really meant was that he did not believe that work can ever contribute to arteriosclerosis or the precipitation of an infarction, his statement was misinterpreted and might lead to a decision not in keeping with our legal precedents.

Is the Patient Telling the Truth?

Many physicians ask themselves the question, How do I know the history given by the patient is correct? The doctor should ordinarily assume that the workman is telling the truth unless he has reason to believe otherwise. When the physician has based his opinion on the history given by the workman, he has satisfied his responsibility.

Testing the truth of the claimant's history is entirely a legal discipline. The attorneys have the weapons of cross-examination, hostile and friendly witnesses, documents and so forth. They are trained in detecting deception. The doctor has no such weapons and no such training. He may properly rely on the patient's history, providing he sets forth in his report what this history is. Should the patient's history be proven incorrect, this does not reflect on the doctor. All sophisticated referees recognize that a doctor's opinion can only reflect the information he has available to him.

An opinion may not be based on *possibilities*. A doctor's opinion becomes meaningful only if it is based on *reasonable medical probability*. This particularly sensitive phrase has never been precisely defined. However, most attorneys believe that its requirements are fulfilled if a doctor, choosing between two alternatives, takes the one he believes has a 51 percent chance or better of being correct. If he chooses between multiple alternative diagnoses, a reasonable medical probability will be satisfied by selecting the most likely diagnosis, provided possibility is substantial, even though it is well below the 50 percent level. Further, court decisions may modify this concept in the future, but at present this is the test put to physicians testifying in this state. It is a reasonable test. It does not demand absolute certainty or even maximally attainable certainty. It requests a sober and careful evaluation of probability or likelihood.

The laws providing care and compensation for the industrially injured workman form an important part of our community structure. They soften the blow of misfortune on the working man, his family, and his orphan. They bring to him better medical care than he ordinarily could afford himself. They give a crippled workman the means and the time to learn a new trade. This humanitarian law depends on the physicians of the community for its performance. It functions best when the most highly skilled and respected physicians of the community evaluate injured workmen and lend their knowledge and experience to the adjudicators.

Advice from Legal Counsel

Refer to: Hassard H: Retention of Medical Records (Advice from Legal Counsel). Calif Med 119:76-77, Nov 1973

Retention of Medical Records

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DUE TO THE ever increasing space requirement for the storage of a patient's medical records, question often arises as to the length of time physicians and hospitals should retain such records. The purpose of this article will be to discuss the pertinent California statutes with regard to medical record retention requirements as well as some practical considerations concerning the possibility of future medical malpractice actions. The term "medical records" covers all of a patient's records including such things as x-ray films, EEG tapes, and the like.

For those physicians and hospitals handling Medi-Cal patients, the Medi-Cal Act requires that the medical records of patients covered by the Medi-Cal Act be retained for a period of three years from the date the service was rendered.

Under the provisions of the Health & Safety Code, the Department of Health is authorized to issue regulations concerning the licensing of hospitals. These regulations, found in Title 17 of the California Administrative Code, require that hospitals retain the records of an adult patient for seven years following the discharge of such a patient. In the case of a minor patient (under 18), hospitals are required to retain the records for one year after the patient reaches majority but never less than seven years. The California Hospital Association has issued detailed recommendations for retention of hospital records.

There are no California statutes that state specifically the requirements for retention of a physician's private records for patients not covered by the Medi-Cal Act. Therefore, the remainder of this article shall cover the retention of medical records with an eye toward the possibility of future medical malpractice actions and the statute of limitations.

The California Code of Civil Procedure [Section 340, Subdivision (3)] formerly provided for a one-year statute of limitations from the date of injury until the filing of a claim. As a result of a series of court decisions, many exceptions were grafted on the one-year statute. For all practical purposes, the statute of limitations was of little aid or comfort to the defendant physician or hospital. In 1970, the legislature amended to some extent the former law. Section 340.5 of the Code of Civil Procedure provides that in an action for injury or death due to the professional negligence of a hospital or physician, the patient must bring the action within four years of the "date of injury or one year after the plaintiff discovers, or through reasonable diligence should have discovered, the injury, whichever first occurs." This four-year period may be extended indefinitely should there be any act of fraud or concealment on the part of a hospital or physician. The courts have previously shown a liberal attitude on behalf of the patient on questions of active fraud or concealment. To date, no appellate court has considered a failure to disclose facts upon which an action could be based as it relates to Section 340.5 of the Code of Civil Procedure. Any future resolution of the question might be influenced by the court's liberality in finding for the patient in questions of active fraud or concealment.

The reader should also be aware that under Section 352 of the Code of Civil Procedure, the statute of limitations is extended if the patient is under certain disabilities, such as minority or insanity. As the new four-year maximum limitation has yet to be tested in the appellate courts, it would be unwise to rely upon it entirely and it is no justification for destroying a patient's medical records.

As a patient's medical records are in many cases the only defense to a malpractice action, it would be wise to retain such records indefinitely, or at least for a minimum seven to ten years after the last day of treatment or the patient's reaching majority, whichever last occurs.

Should the decision be made to retain medical records indefinitely, the question that naturally

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follows is whether the records must be kept in their original form or may be microfilmed in order to reduce space requirements.

The California Evidence Code permits the use of microfilmed records if made in the "regular course of business." The Code also permits the admissibility of photographic copied records when the originals have been lost or destroyed. In addition, the Evidence Code provides an alternative method should the records not be shown to be "business records." A "certification" attached to a sealed container holding the film, or incorporated in the film itself will permit the use in court of photographic copies.

The net result of the foregoing inquiry is to recommend that a patient's medical records be retained indefinitely due to malpractice considerations, as well as the need of the records for further treatment by the physician or subsequent treating physician; but in order to substantially reduce the enormity of space requirements and facilitate the locating of specific records, they be microfilmed for storage purposes.

Refer to: Willett DE: Medical records—The patient's right to information (Advice from Legal Counsel). Calif Med 119:77-79, Nov 1973

Medical Records

The Patient's Right to Information

DAVID E. WILLETT, Esq., *San Francisco*

QUESTIONS ABOUT a physician's obligation to provide copies of his medical charts or information from them come frequently to attorneys who counsel the medical profession. Under the law, medical records belong to the physician. Moreover, there are strong legal and ethical requirements that medical records be kept confidential. But there are also legal and ethical requirements obliging physicians to provide information from medical records, or even copies of the records.

As a general rule, information in a patient's medical record cannot be released without his consent. The Medical Practice Act (Business & Professions Code §2379) provides that the willful betraying of a professional secret constitutes unprofessional conduct. The most common exception to the rule prohibiting disclosure without patient consent arises if the physician is served with a subpoena. A subpoena is a court order requiring the production of documents or the giving of testimony, and must be obeyed unless the court reconsiders its order. When production of medical records or disclosure of information would be injurious to the patient's health, or harmful to innocent family members or third parties, application may be made to the court for a protective order restricting disclosure.

Other exceptions to the general obligation to maintain confidentiality arise from statutory requirement for the reporting of such conditions as communicable diseases, injuries caused by criminal conduct, diseases characterized by lapses of consciousness, and the like. In these instances, patient consent is not required, and otherwise confidential information must be disclosed.

What about the other side of the coin? Must information be provided upon the request of a patient? It is likely that the courts will hold that patients are entitled to the *information* contained in their records. The California Supreme Court case of *Cobbs* v. *Grant,* dealing with informed consent, stresses the patient's "right to know." A patient probably has no legal right to see his own medical record. The chart itself is maintained for the physician's use, and permitting the patient access to his chart does not necessarily enhance his knowledge. It may even be misleading to the lay person. More importantly, the purpose of any medical record is to protect the patient's health, and physicians know that there are circumstances in which this primary consideration would be violated if the patient were held to have a right of access to the chart itself.

The Legislature has declared that a patient's *attorney* must be given an opportunity to see and copy all of the patient's medical records, with the patient's consent. In those instances where the patient or third parties would be hurt by knowledge or disclosure of information in the record, this should be brought to the attention of the attorney. In most cases, attorneys will exercise great discretion in protecting against such injury, particularly since the attorney himself may have some legal duty in this regard. Evidence Code

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§1158 requires that all medical records be made available during business hours for inspection and copying within five days after the attorney's presentation to the physician of the patient's written authorization. The physician need not permit the removal of the records from his office, and ordinarily should not do so. The attorney cannot be required to pay for the privilege of viewing and copying the records, although reasonable copying charges are applicable if the attorney requests the physician to make the copies.

Otherwise, the physician's obligation to provide information at the patient's request is determined within the bounds of the physician-patient relationship. Certainly, the patient should be given information about a present condition or course of treatment. This arises from the need for informed consent, and to avoid the kind of misunderstandings which lead to a breakdown in the physician-patient relationship. More troublesome are requests for information about past treatments or past events. Such requests may come from other physicians, or from insurance companies.

The AMA Judicial Council's *Opinions and Reports* discuss the physician's ethical obligation:

> The interest of the patient is paramount in the practice of medicine, and everything that can reasonably and lawfully be done to serve that interest must be done by all physicians who have served or are serving the patient. When a colleague who is presently treating a patient requests records from another physician who has formerly treated the patient, that former physician should promptly make his records available to the attending physician . . . the manner of making the report—or the information contained therein—available to the succeeding physician is immaterial and will depend on the circumstances of each case.

A further holding states:

> It is unethical for a physician, who formerly treated a patient, to refuse *for any reason* to make his records of that patient promptly available on request to another physician presently treating the patient.

This statement of ethical principle also reflects a requirement of good medical practice. It is recognized that the physician's obligation to his patient may extend even after the physician-patient relationship has terminated. A physician who refuses *for any reason* to make necessary medical information available to subsequently treating physicians may be held to have violated legal obligations, as well as ethical requirements. If any injury results which the availability of such information might have avoided, the physician who refused to provide information may be liable in damages. Even if the patient has been unconscionable in his attitude toward the physician—as in those cases where he has made no effort to attend to outstanding bills—the physician faces a real risk if he fails to honor requests for information needed by other medical practitioners.

The obligation to provide information apparently extends also to information required by insurance carriers. A Delaware court ruled this year (303 A.2d 668) that the relationship between doctor and patient is "fiduciary in character," and the physician's obligation can include the duty to complete insurance forms. In that case, the court refused to interfere with a trial on the issue of whether or not a physician was personally liable for very substantial medical expenses sustained by a patient, when the patient was uninsured because of the doctor's allegedly negligent failure to complete insurance application forms, after many requests from the patient. The court suggested that the physician at least had the obligation to refer the patient to another source for the needed information (assuming that another source existed). AMA's Judicial Council states:

> The attending physician should complete without charge the appropriate "simplified" Health Insurance Council forms approved by the Council on Medical Service, and similar insurance claim forms as a part of the physician's service to the patient to enable him to receive his benefits. A charge for more complex forms may be made in conformity with local custom. This suggestion is advisory. In all cases, the local medical society can be looked to for an authoritative opinion.

An insurance company seeking medical information should be required to provide the patient's consent. If this consent is provided, there is an obligation to provide necessary information. If the consent form bears a "stale" date, more timely consent may be requested. A physician who feels that the insurer may not have obtained the patient's "*informed* consent" may elect to discuss the request with the patient.

The physician may use his discretion in determining whether or not to make his chart available to the insurance company, and he may object to requests which seek clearly unnecessary information, but requests from insurance companies should not be ignored. Insurance company requests to photocopy medical records may be refused, but the physician must offer a reasonable alternative in providing information from his records.

It is generally considered inappropriate to charge for responses to simple requests, except perhaps for actual copying charges.

Summary

Except in special circumstances, patient consent is required for the disclosure of medical information. When a patient has requested that information be provided, there is a legal and ethical obligation to comply if there is a reasonable purpose behind the request. Only information necessary to that purpose need be produced, and the physician can usually determine the manner of compliance, so long as it is reasonable. A patient's failure to pay outstanding bills will not of itself support a refusal to provide information which has been requested and which would otherwise be made available.

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Refer to: Flynn PF: Criteria for levels of care evaluation under Medicare (Government and Medicine). Calif Med 119: 80-84, Nov 1973

Criteria for Levels of Care Evaluation under Medicare

PAUL F. FLYNN, MD, *Oakland*

SINCE PATIENTS or their families sometimes look on Medicare as an agent that will pay for almost limitless medical services, informed physicians can better serve their Medicare patients by helping them understand the limitations as well as the benefits of the program. In the end the additional burden that this puts upon the physician and his office personnel may prove well worth bearing.

It may be that, as physicians, we can help change the law and regulations and extend the scope of Medicare by appropriate communication with lawmakers, but until such time as changes are made, we must function within the program. And in doing so, we must keep our patients advised of what benefits they are entitled to under the program, and, where necessary, when such benefits may cease. To properly advise patients and their families, however, we must have adequate understanding of Medicare—something I suspect many of us do not have.

The fiscal intermediaries for the Medicare program have continued to offer education and assistance to hospitals and physicians participating in the program, but staff presidents and utilization review committee chairmen report that too often when such educational meetings or seminars are offered, those who need them most do not attend.

Possibly part of the reason for disinterest in such educational programs is a belief that the fiscal intermediaries give no consideration to the opinion of the attending physician or the utilization review committee in deciding what is or is not covered by Medicare. This is not true. Weight is given to the opinions of both; and many times, with these opinions in mind, a disputed case may be considered as covered care. Where there is disagreement, the problem often lies in a lack of understanding of the levels of care under Medicare and the limitations of the program. Utilization review committees are encouraged to implement ongoing review, to discuss problem cases early with attending physicians, and to make use of the educational assistance of the fiscal intermediary.

Know the Medicare Law

The Medicare law, administered by the Social Security Administration, has given the fiscal intermediaries the responsibility for making payment to providers of service only for those covered levels of care. In abiding by their contractual agreement with the Social Security Administration, the fiscal intermediaries must conduct a continuing review of Medicare claims to determine that they meet criteria set forth in the Medicare law. Before claims are paid, they must be reviewed to make sure they meet the requirement for levels of care.

In order to avoid misunderstandings and to

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Submitted May 29, 1973.

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meet their obligations to their patients, physicians must have an understanding of the Medicare scope of coverage. With that understanding, physicians can help their patients avoid the unexpected burden of payment on claims that probably will be totally or partially denied payment.

Role of Physician Consultants

Using the guides outlined above, physician consultants who are practicing physicians in the community, advise the fiscal intermediary in disputed cases concerning the appropriate levels of care. A case is never disallowed unless it is reviewed by a physician consultant. Only a small proportion ever reach the final level of physician review.

The Importance of Medical Documentation

No matter what the level of review—acute hospital, skilled nursing facility or home health agency—the utilization review committee, the county medical society or the reviewer for the intermediary must have clear documentation of the patient's need for receiving specific levels of care. Again, this requires understanding the levels of care, the limitations of the program, and the realization that Medicare was not intended to function and does not function as a socio-economic program, but one devoted to acute care.

The necessity for medical care, then, should be clearly noted in the histories, physical examinations, orders and progress notes on the patient. Diagnoses are important, but the reviewer's attention will focus on specific levels of care ordered for the patient.

It is believed that the best review can be done at the local level, but to be effective it must be timely and thorough and conducted with a full knowledge of the intent of Medicare.

Medicare "Guidelines"

Utilization review committees, medical societies and attending physicians continue to ask for the Medicare "guidelines" developed by the intermediary. As with any guidelines, those for the Medicare program are no more than suggestions or statistically engendered limits. They cannot be rigid when applied to medical care. The guidelines used by the fiscal intermediary are utilized primarily to allow more rapid processing of the bulk of the cases. Services within the limits of coverage are paid and those outside are referred to physician consultants for individual case consideration.

If guidelines were to be released by an intermediary, they might easily become inflexible rules and thus actually add another restriction to the attending physician's activities. From the medical point of view, it is quite obvious that each case must be decided on its own merits, and only the attending physician can determine how long a patient needs any level of care. The publication of guidelines tends to solidify them and hence remove this function from the attending physician. In such circumstances a rigid code could limit the care to less than the physician feels a patient needs.

A physician who understands Medicare and levels of care should need no guidelines. He knows his patient, he clearly documents the patient's needs, and in fact sets his own guidelines based on his own experience.

As more physicians become aware of the benefits and the limitations of the Medicare program, retroactive denials of payment on claims will become less frequent. And patients whose physicians keep them apprised of program coverage will benefit from a more knowledgeable use of the Medicare program when medical care is needed.

Levels of Care Defined

The Medicare program provides for the acute medical care needs of patients in the over age 65 group. The "benefit" period begins when the attending physician admits a patient to the hospital because, medically, the patient's need is for that level of care. Levels of care are the major areas of concern and major reasons for reviews for payment in today's Medicare program.

Evaluation of the levels of care needed by a patient is only one part of the determination of "covered" versus "noncovered" services under the Medicare law. Other variants must also be considered, such as the appropriateness of the following: (1) the location of the patient, (2) the services provided, (3) the timing (sequence) of services, and (4) the amount of services.

Claims may be denied because of the inappropriateness of any of these. For example, delay caused by a physician's failure to contact a consultant or to obtain laboratory or x-ray studies, unless *documented* as medically necessary, will result in the patient's hospital stay during this delay to be considered "noncovered" and, therefore, not payable by Medicare.

Under Part A of the Medicare program, an (1) acute hospital, (2) skilled nursing facility (formerly called "extended care facility") or (3) home health agency is certified as a provider of service by the state licensing agency (California Bureau of Licensing and Certification). Providers receiving such certification must have met Federal requirements for participation in Medicare.

Level of care is a specification of the need that a patient has for three services: (1) physician services, (2) skilled nursing services, and (3) acute hospital services. Each location—that is, acute hospital, skilled nursing facility or home health agency—has a specified level of care available only at that location. An evaluation of the level of care specified by the above three services assists the intermediary's reviewers in deciding on the appropriateness of the patient's location and the services received at that location. Evaluation of the appropriateness of services, their timing and amount is assumed to have been done in the evaluation of the level of care. And, when conducting review and evaluation of levels of care, it is assumed the services ordered by the attending physician were appropriate.

Detailed descriptions and examples illustrating the various levels of care are developed in the following discussion to assist physicians in proper documentation of services to Medicare beneficiaries.

Care in Acute Facility

Care in an acute hospital is the first Medicare level of care. It is available when the attending physician determines he is unable to treat or diagnose the patient's condition outside the hospital. Care in the acute facility must first be determined reasonable and medically necessary, and documentation of the medical necessity should be provided by the attending physician.

The physician's plan of treatment for a patient admitted to the acute hospital must include: (1) the continued availability of medical supervision (physician) or other medical consulting staff, (2) the continuing availability of licensed nursing personnel, and (3) the immediate availability of other diagnostic or therapeutic services and equipment ordinarily available only in an acute hospital setting.

For acute facility care, the patient is entitled to 90 days per benefit period. In addition, the patient may draw upon his nonrenewable 60 "lifetime reserve" days, if medically necessary and if treatment of his condition meets all of the above three requirements.

When the level of care changes from that covered in a hospital, but the patient still needs skilled services, the physician should consider other available health facilities which would be covered by Medicare. The attending physician and the hospital's utilization review committee should review the case, considering appropriateness of the patient's location, services received, timing of services, and amount of services.

In all cases, planning for discharge of the patient from the acute facility should be considered upon admission, or as soon thereafter as possible. To reduce patient's apprehension about out-of-pocket expense, such planning is intended to eliminate, insofar as possible, hospital stays that are noncovered under Medicare regulations.

Skilled Nursing Facilities (SNF)

For a patient to be eligible for Medicare benefits in a skilled nursing facility, he must have been in an acute hospital for three consecutive days (the day of discharge is not counted) and his hospital stay must have met the criteria for payment by Medicare. A patient admitted to a skilled nursing facility must require services that are provided directly by or require the supervision of skilled nursing personnel, or skilled rehabilitation services which the patient needs daily and which as a practical matter can only be provided in a SNF on an inpatient basis.

This care must be for the same illness or injury for which he was admitted to hospital. Specifically, the discharge diagnosis from the acute hospital should be the admitting diagnosis recorded upon admission to the extended care facility.

Care in the skilled nursing facility is the second level of care available after a patient has spent a period of at least three consecutive covered days in an acute facility. Although known and described as post-hospital extended care, subacute or a lower level of care, it is recognized as equal in importance to acute hospital care as it relates to the total treatment of the patient. Admission to the skilled nursing care facility continues the patient's benefit period that began in the acute hospital.

For admission (not transfer) to a skilled nursing facility, the patient must (1) need a level of care providing continuing availability of skilled nursing or rehabilitation services but no longer need the constant availability of physician services or acute ancillary services provided by a hospital; (2) have met a three-day qualifying stay in the acute hospital; and (3) must be admitted to the skilled nursing facility within 14 days after discharge from the acute hospital.

The patient is entitled to 100 days of care per benefit period in a skilled nursing care facility if the medical necessity is primarily for continuous availability of skilled nursing care. Because the major requirement for coverage of skilled nursing care facilities is skilled nursing service, the following definition is provided to aid in determining patient admission to the skilled nursing care facility.

Skilled Nursing Service

Skilled nursing service must be furnished under the general direction of a physician in order to assure the safety of the patient and to achieve the medically desired result, and such service must be given by or under the direct supervision of licensed nursing personnel.

Skilled nursing service includes: (1) assessment of the total needs of the patient and planning and management of a patient care plan, (2) provision of direct services to the patient where the ability to provide services requires specialized training,* and (3) observation and monitoring of the patient's response to care and treatment.

Thus, the controlling factor in determining whether a person is receiving covered care is the level of care and medical supervision that the patient requires, rather than considerations such as diagnosis, type of condition or degree of functional limitation.

Under the Medicare program, skilled nursing care facilities should not be mistaken for nursing homes, long-term care, or intermediate care facilities. A skilled nursing facility is certified and licensed by the state agency for a specific level of care. It may also be licensed as a nursing home or long-term facility, but these designations are indicated separately. Such designations for licensing are important for another reason—the determination by the physician of the appropriate level of care for his patient.

If the primary purpose of total care provided an individual in a skilled nursing care facility is to assist him in meeting the activities of daily living, the custodial care exclusion applies and no payment can be made under the Medicare program for any of the care provided. Thus, a patient may be a Medicare beneficiary in a skilled nursing facility until his level of care changes to custodial-type care, at which time Medicare coverage ceases. Where the services are needed for rehabilitation, benefits are available if services are active, ongoing and necessary for patient care, according to Medicare regulations.

Medical Care in the Skilled Nursing Care Facility

Physicians' visits to a skilled nursing care facility must be reasonable and meet the needs of the patient. Covered extended care under the Medicare program is recognized by the fiscal intermediary *only* when documentation substantiates the medical necessity and frequency and observations of the skilled nursing services required. Here again, the physician must evaluate his patient's care to determine that the patient is in the right place at the right time and is receiving the right services.

Evaluation of medical care at all levels of a patient's treatment is an important part of the Medicare program. The Medicare law requires utilization review committees at the skilled nursing facility level, as it does in the acute hospital. Each case should be carefully reviewed at the time of admission and during the stay to determine that the patient continues to need the constant availability of skilled nursing care or rehabilitation services. On-site review by members of the utilization review committee, performed in a timely manner, can reduce the number of retroactive denials.

Home Health Agencies

Service from a home health agency provides the third level of care, and its benefits are available if the patient has been in a hospital for three consecutive days or in a skilled nursing facility *after* a three-day hospital stay. (See section on *admission,* not transfer to a skilled nursing care facility). The attending physician's decision that a patient needs continued care best given in the home by a home health agency (HHA) continues the benefit period which began in the acute hospital. As many as 100 home health agency visits are available after the start of one benefit period and before the beginning of another.

While the physician must determine the medical need for home health care, the plan of treatment *must* be established within 14 days after discharge from the acute hospital or participating skilled nursing facility. Visits to a patient must be medically necessary and be provided by a participating home health agency.

Under the Medicare program, services of a home health agency are covered if they are medically necessary and are available, provided the following conditions are met: (1) the patient was in a participating (or otherwise qualified) hospital for three consecutive days, (2) the continuing care needed includes part-time skilled nursing care or physical or speech therapy, (3) the patient is confined to home, and (4) the home health agency care is for further treatment of a condition for which services were provided in the acute or extended care facility.

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*Medicare Fact Sheet—SSA, BHI/Baltimore, MD 21235—July, 1972.

If the attending physician has determined that the patient is eligible for the qualifying benefits mentioned above, other home health agency services may also be covered, such as (1) occupational therapy, (2) part-time services of home health aides, (3) medical social services, and (4) medical supplies and appliances furnished by the agency, such as physical therapy.

Physician Understanding of HHA Services

Home health agency services are often misunderstood and sometimes unknown to the physician, although they provide a valuable level of care. Elderly patients who may be uncomfortable in the strange settings of hospitals or skilled nursing facilities may find home health agency services beneficial. If the condition of these patients does not require the acute or extended care level of medical supervision and care, recovery at the home level and the availability of home health services should be considered. Physicians should consider utilization of home health agency services in their early discharge planning.

Home health agency services described above are also available under Medicare Part B without the need for the qualifying stays.

Alternate Levels of Care

One problem in the reluctance of physicians to send patients to an alternate or lower level of care is that they lack confidence in facilities other than acute hospitals. This problem is particularly evident when patients are considered for admission to a skilled nursing facility.

There are many excellent skilled nursing facilities available for the needs of Medicare patients. If there are some that do not offer what the attending physician desires for his patient, then the physician, his county medical society and, if need be, even the state medical association, can act to correct this situation. The quality of the skilled nursing facility is something the physician should be involved in quite as much as he is in the acute hospital.

In any case, where the patient should clearly have been admitted to a skilled nursing facility, the fiscal intermediary is prevented from paying for coverage at the acute level.

Knowledge of the Medicare law by the physician can greatly enhance his ability to provide the best possible medical care for the Medicare patient and to forewarn of unexpected costs to be borne by the patient. Through physician understanding of the Medicare law, patients will have access to levels of care designed to best meet their health care needs.

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Information

CLINICAL CARDIOLOGY SERIES

The Assessment of Myocardial Infarction with Serum Enzyme Determinations

WILLIAM E. SHELL, MD

Material Supplied by the American Heart Association

ELEVATED SERUM ENZYME activity has become a cornerstone in the diagnosis of acute myocardial infarction. The absence of elevations when carefully sought for is an excellent criterion for exclusion of the diagnosis. Recently, investigative effort regarding serum enzyme elevations in patients with acute myocardial infarction has been directed toward the use of such determinations as indices of prognosis and specifically as a means by which the extent of ischemic myocardial injury can be quantified. Rapidly accumulating evidence suggests that prognosis after acute myocardial infarction is related to the extent of myocardial necrosis and that this in turn is reflected quantitatively by the magnitude of alterations of serum enzyme activities.

In experimental studies in the 1950's it became clear that a general relationship existed between peak serum enzyme activity following coronary occlusion and the extent of myocardial necrosis assessed morphologically. Experimental myocardial infarction produced in open chest or closed chest preparations consistently led to elevated serum enzyme activity in serum. In general small infarcts were associated with low peak levels of serum glutamic oxalic transaminase (SGOT) and lactic dehydrogenase (LDH) and large infarcts were associated in high peak levels. However, peak levels of these and other enzymes exhibited considerable variation in animals with infarcts of comparable size; hence in individual animals determination of peak enzyme activity does not permit reliable estimation of infarct size measured pathologically. This variation is due in part to the effects of surgical interventions utilized in producing the experimental infarction on the activity of serum enzymes, biological variation in the rate of enzyme release from ischemic myocardium, and nonuniform ischemic injury within the infarct itself.

Despite these limitations, considerable evidence indicates that the magnitude of peak serum enzyme activity following myocardial infarction presages prognosis. After spontaneous myocardial infarction in man SGOT begins to rise, usually within 12 hours, and reaches a peak level within 24 to 36 hours. Peak SGOT values greater than 300 Karmen units (KU) have been associated with adverse prognosis and with a mortality of 40 percent within the first six weeks. On the basis of autopsy studies it is apparent that a linear relationship exists between gross morphologic estimates of infarct size (small, medium, and large) and the magnitude of serum enzyme elevations. Thus, patients dying with small infarcts exhibited an average peak SGOT of 100 KU compared to 180 KU in those with medium infarcts and 450 KU in those with large infarcts. It is likely, that hepatic release of SGOT, reflecting congestive heart failure, contributes to the marked elevations seen in patients with large infarcts.

Serum lactic dehydrogenase activity bears a similar relationship to infarct size. Peak LDH levels of greater than 150 units per ml are associated with increased risk and apparently large infarcts. A level of serum alphahydroxybutyric acid dehydrogenase (HBD), reflecting the activity of isoenzymes of LDH typical of those seen in heart muscle, exceeding 800 international units (IU) per ml has been associated with mortality rates of 30 percent while a level less than 800 IU per ml has been associated with a mortality rate of 15 percent or less. It is important to recognize that LDH activity in serum frequently reflects extraneous sources of enzyme, particularly the red cells which release large quantities of LDH into serum with even minimal hemolysis.

Serum creatine phosphokinase (CPK) activity appears to be a good index of prognosis. Peak serum CPK activities exceeding 600 mIU per ml are associated with mortality rates greater than 30 percent while values less than 600 mIU per ml (12 times normal) are associated with a risk of only 12 percent. It has been found that peak values less

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Dr. Shell is from the Department of Medicine, University of California, San Diego, School of Medicine.

than 300 mIU per ml are associated with mortality rates of only 2 percent. Results of CPK determinations are dependent upon the specific assay employed and become meaningful only when the assay is performed with careful attention to technique.

Morbidity as well as mortality appeared to be related to the magnitude of peak serum enzyme activities following myocardial infarction. Major arrhythmias such as ventricular tachycardia, ventricular fibrillation, and A-V block occur much more commonly in patients with high peak serum enzyme activities. Severe hemodynamic abnormalities also appear to be more common in patients with high enzyme values. Moreover, the hemodynamic abnormalities may persist for several months or indefinitely in those patients with high serum enzyme values associated with an episode of acute infarction. Patients with marked serum enzyme elevation are likely to show increases in left ventricular end diastolic pressure during the acute phase and frequently progression of these abnormalities during succeeding months. Wall motion disorders are also more common in those patients with marked elevation of serum enzyme activity. It appears likely that the electrophysiological, physiological, and prognostic features associated with marked elevation of serum enzyme activity after acute myocardial infarction are all related to infarct size, in turn reflected by the magnitude of peak enzyme elevation.

The peak level of enzyme activity observed after acute myocardial infarction depends on several factors including: (1) frequency of sampling, (2) the rate of enzyme release from myocardium, (3) the rate of enzyme clearance from the circulation, (4) the volume into which the enzyme is distributed, (5) contributions from extraneous non-cardiac sources of enzyme, and (6) infarct size. In order to relate enzyme changes appropriately to infarct size and to prognosis, these factors must be taken into consideration. In patients with acute myocardial infarction samples for enzyme determinations at least every 12 hours are helpful in assessing trends and in determining the actual peak level. Intramuscular injections should be kept to a minimum in order to reduce the likelihood that extraneous sources of enzyme will cloud the picture. Blood specimens must be obtained with thorough precautions to avoid hemolysis. Isoenzyme determinations should be employed to facilitate interpretation of elevated enzyme activities.

Since the observed levels of enzyme activity in blood in part reflect infarct size, serum enzyme analysis may offer a more precise means of estimating the extent of myocardial injury associated with a specific episode of infarction. We have recently utilized serial changes in serum CPK activity to measure infarct size in patients. The approach is based on a mathematical model which takes into account the rate of CPK release, CPK clearance, and the plasma volume into which CPK is distributed. In animal experiments we have observed a close correlation between infarct size assessed from serum CPK changes analyzed with the use of this model and infarct size measured directly by analysis of myocardial CPK depletion. In patients, assessment of infarct size by serial serum CPK analysis has served as a reliable index of subsequent mortality and morbidity. In patients with estimated infarct size exceeding 50 CPK-gram-equivalents, acute mortality (within 30 days) was 36 percent compared with 3 percent in those patients with infarct size less than 50 CPK-g-eq. Long term mortality and morbidity was similarly related to CPK-infarct size. In patients followed for six to twelve months, 67 percent of those with infarct size exceeding 65 CPK-g-eq were either dead or Class III or IV. Thus, analysis of serial enzyme changes has proven useful in the assessment of infarct size, in turn a valuable index permitting separation of patients according to risk.

Summary

Peak SGOT, LDH, and CPK levels are related to prognosis after acute myocardial infarction. Peak serum enzyme activity and prognosis correlate probably because they are both related to infarct size. Infarct size can be estimated reliably in patients by mathematical analysis of serial serum CPK changes. This approach permits improved assessment of risk in specific patients with acute myocardial infarction and should prove valuable not only in facilitating the management of individual patients but also in conducting clinical trials to assess mortality related to therapy with potential risk. Clinical enzymology is no longer merely a tool for the recognition of acute myocardial infarction but is rapidly becoming applicable as an important means for assessing the severity of the infarction and estimating prognosis reliably.

In Memoriam

Bolzendahl, Walter H., San Francisco. Died September 5, 1973 in San Francisco, aged 38. Graduate of the Universität Zurich, Medizinische Fakultät, 1963. Licensed in California in 1965. Doctor Bolzendahl was a member of the San Francisco Medical Society.

⁂

Buckley, Daniel Noel, Tulare. Died September 17, 1973, aged 62. Graduate of the Creighton University School of Medicine, Omaha, 1934. Licensed in California in 1934. Doctor Buckley was a member of the San Francisco Medical Society.

⁂

Crossan, John Wesley, Los Angeles. Died May 20, 1973 of cancer, aged 90. Graduate of St. Louis University School of Medicine, 1911. Licensed in California in 1911. Doctor Crossan was a member of the Los Angeles County Medical Association.

⁂

Crow, Thayer A., Lemon Grove. Died September 16, 1973, aged 64. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1949. Licensed in California in 1949. M.D. degree from California College of Medicine, 1962. Doctor Crow was a member of the San Diego County Medical Society.

⁂

Donnelly, Thomas E., San Francisco. Died September 10, 1973 in Truckee, aged 47. Graduate of the Creighton University School of Medicine, Omaha, 1953. Licensed in California in 1954. Doctor Donnelly was a member of the San Francisco Medical Society.

⁂

Gladstone, Albert L., Northridge. Died September 6, 1973 in Granada Hills, aged 62. Graduate of the Univerity of Louisville School of Medicine, 1936. Licensed in California in 1947. Doctor Gladstone was a member of the Los Angeles County Medical Association.

⁂

Higbee, David Rothburn, San Diego. Died July 25, 1973 in San Diego, aged 85. Graduate of Cornell University Medical College, New York, 1917. Licensed in California in 1922. Doctor Higbee was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

Irwin, Leslie, Long Beach. Died May 9, 1973 of myocardial infarction, aged 56. Graduate of New York University School of Medicine, New York, 1941. Licensed in California in 1948. Doctor Irwin was a member of the Los Angeles County Medical Association.

⁂

Joseph, Peter S., San Francisco. Died September 2, 1973 in San Francisco of heart disease, aged 61. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1940. Licensed in California in 1940. Doctor Joseph was a member of the San Francisco Medical Society.

⁂

Kenniker, Eldine Loraine, Santa Barbara. Died August 23, 1973 in Santa Barbara, aged 46. Graduate of Northwestern University Medical School, Chicago, 1954. Licensed in California in 1960. Doctor Kenniker was a member of the Santa Barbara County Medical Society.

⁂

Magan, Wellesley Percy, Sr., Covina. Died September 9, 1973, aged 80. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1918. Licensed in California in 1918. Doctor Magan was a member of the Los Angeles County Medical Association.

⁂

Mikita, Michael M., Sonoma. Died September 2, 1973 in Sonoma of cancer, aged 58. Graduate of Rush Medical College, Chicago, 1941. Licensed in California in 1941. Doctor Mikita was a member of the Sonoma County Medical Association.

⁂

Newgard, K. Warren, San Francisco. Died September 24, 1973 in San Francisco, aged 64. Graduate of the Université de Genéve Faculté Médecine, 1934. Licensed in California in 1936. Doctor Newgard was a member of the San Francisco Medical Society.

⁂

Pritchard, Jacob Leroy, Santa Clara. Died September 1, 1973 in San Jose, aged 88. Graduate of the University of California Medical School, Berkeley-San Francisco, 1916. Licensed in California in 1916. Doctor Pritchard was a retired member of the Santa Clara Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

Savage, John C., Tulare. Died August 18, 1973 in Tulare, aged 51. Graduate of the University of Southern California School of Medicine, Los Angeles, 1955. Licensed in California in 1956. Doctor Savage was a member of the Tulare County Medical Society.

⁂

Stephens, Joseph M., Victorville. Died September 10, 1973 near Apple Valley of injuries received in an automobile accident, aged 61. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1951. Licensed in California in 1951. M.D. degree from California College of Medicine, 1962. Doctor Stephens was a member of the San Bernardino County Medical Society.

⁂

Windesheim, John Henry, Berkeley. Died August 31, 1973 of injuries received in an automobile crash near Live Oak, Butte County, aged 47. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1952. Licensed in California in 1953. Doctor Windesheim was a member of the Alameda-Contra Costa Medical Association.

⁂

Zumwalt, Elmo Russell, Tulare. Died September 5, 1973 in Seattle, aged 81. Graduate of University of California Medical School, Berkeley-San Francisco, 1917. Licensed in California in 1917. Doctor Zumwalt was an honorary member of the Tulare County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

MEDICAL SPECIALTY TERMINOLOGY—X-Ray and Nuclear Medicine—Volume Two—Clara Gene Young, Retired Technical Editor and Writer (Medical), U.S. Civil Service, former Instructor, Medical Terminology, Good Samaritan Hospital, Phoenix; Joseph J. Likos, MD, Chief, Laboratory Service and Nuclear Medicine, Veterans Administration Hospital, Phoenix. The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Mo. (63141), 1972. 283 pages, with 124 illustrations, $15.75.

A bona fide need has existed for a current compendium of medical specialty terminology in radiology. Such a book is now available, thanks to Ms. Young and Dr. Likos. Editors, secretaries, student technicians, and nurses will find this small book quickly answers many terminology questions in a terse and direct manner.

The x-ray terminology portion of the book is organized by systems, an organization that seems particularly appropriate to the subject. The nuclear medicine section consists of a brief introduction, a chapter on how radioisotopes are used in medicine, a chapter describing specific radiopharmaceutical applications, and a glossary of terminology pertaining to x-ray and nuclear science. It is only this 8-page glossary which directly addresses the topic of the book and is organized in the same way as the section on diagnostic radiology.

There are some other major organizational lapses, such as the inclusion of the major discussion of the thymus under endocrine rather than thoracic diseases, of the blood under cardiovascular and lymphatic systems.

Hopefully, future editions will be improved by including current neonatal terminology which is conspicuously absent. Entities such as idiopathic respiratory distress syndrome, bronchopulmonary dysplasia, meconium aspiration, transient tachypnea of the newborn, and erythrocythemia are not mentioned at all. Line drawings or labeled roentgenograms would have enhanced the text and are sorely needed, for in many cases the illustrations are so briefly described as to be of limited value. Some illustrations are excellent, others are most inadequate.

The review of nuclear medicine terminology was unfortunately brief. The *in vitro* assays (radioimmunoassays and displacement assays) were neglected. The only word listed to describe radionuclide imaging or scintigraphy was "scanning," an incorrect although frequently used designation for scintiphotography with a stationary detector device.

Bibliographical references are quite out of date in some chapters but are generally useful. For example, 80 percent of the references on the respiratory section are 10 to 15 years old.

In summary, this book will provide many people with a manageable source for terminology of diagnostic radiology despite many deficiencies.

CHARLES A. GOODING, MD
MALCOLM R. POWELL, MD

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ARTIFICIAL ORGANS AND CARDIOPULMONARY SUPPORT SYSTEMS—Editors: Felix T. Rapaport, MD, Professor of Surgery, New York University Medical Center, New York; John P. Merrill, MD, Professor of Medicine, Harvard Medical School, Boston. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003) 1972. 186 pages, $15.00.

This timely symposium provides the reader with a frank overview of the current status of artificial organs and support systems, together with an evaluation of clinical experiences by leading investigators in the field. With the vast proliferation of new information concerning artificial organ technology during the past five years, it has been difficult for most physicians to maintain more than a superficial familiarity with current developments. This volume should, therefore, be of interest not only to those engaged in organ transplantation but also to all physicians in clinical practice.

The first section of the book summarizes the history, current status, and anticipated future developments of the artificial kidney. The authors conclude that patients with chronic renal failure should be treated with dialysis at an early stage rather than after severe symptoms occur. Home dialysis is preferable to dialysis in a medical center both from the standpoint of the patient's well-being and cost. Future artificial kidneys probably will be smaller, more compact models that utilize atraumatic and nonthrombogenic membranes.

The second section of the book deals with the development and use of membrane oxygenators. Of the currently available membranes, silicone copolymers are the most effective. As with other artificial organs, damage to blood by contact with foreign materials and thrombogenesis remain major problems. Most currently used oxygenators are capable of exchanging 50 ml of oxygen per square meter per minute. A new oscillating (toroidal) flow oxygenator under study appears to have great promise in that it can exchange oxygen at four times the rate of previous oxygenators. Respiratory support systems have been used for several clinical patients, although the long-term survival has been low. The criteria for selection of patients for treatment remain somewhat unclear. Major problems still to be resolved include sepsis, damage to blood, and hemorrhage with prolonged heparinization.

In a section on artificial hearts, it is indicated that the auxiliary left ventricle has been discarded in favor of the total implantable mechanical heart. Both smooth and rough prosthetic surfaces are under study to decrease the problems of clotting. Thromboembolism and disseminated intravascular coagulation due to multiple small thromboemboli appear to produce diffuse clotting and a fibrinolytic syndrome. Inadequate cardiac output has been one of the most common and serious limitations.

Intraaortic balloon pumping with both permanent and temporary devices has been successful in a small number of patients and may be helpful in supporting a patient after a myocardial infarction or following cardiac surgery. External counter pulsation devices that utilize both positive and negative pressure have shown promise in supporting the failing circulatory system.

In a separate chapter, Salzman presents an excellent general review of the problems of clotting and of thrombogenic surfaces. Intact endothelium is the only real nonthrombogenic surface yet available.

The next series of chapters is devoted to alimentary and metabolic life-support techniques and details many of the new solutions, catheters, and pumps which have been used to reduce complications and increase efficiency.

Another section of the book deals with the treatment of liver failure by various techniques. Extracorporeal infusion of the intact liver in the pig or baboon has had some success; however, exchange transfusion may be more feasible. Repeat perfusions have been necessary in most patients over a period of at least three months, and sepsis has been a major problem.

In the final section new techniques of skin replacement using the synthetic membrane polytetrafluoroethylene are discussed and appear to offer promise in the severely burned patient. Current progress in organ preservation, banking, and freezing are also presented.

This highly informative, well-written symposium is the best review of the field of artificial organs and support systems currently available.

ERIC W. FONKALSRUD, MD

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CURRENT PEDIATRIC DIAGNOSIS AND TREATMENT—Second Edition—C. Henry Kempe, MD, Professor of Pediatrics and Chairman, Department of Pediatrics; Henry K. Silver, MD, Professor of Pediatrics; and Donough O'Brien, MD, FRCP, all from the University of Colorado School of Medicine, Denver; and Associate Authors. Lange Medical Publications, Drawer L, Los Altos, Ca. (94022), 1972. 1,008 pages, $12.00.

This second edition of a book first published in 1970 is an up-to-date guide to pediatric treatment, diagnosis and physical examination. It should be particularly useful to pediatric house officers and young pediatricians for whom it is largely intended. Its approach is a practical one reflecting the clinical experience of its University of Colorado Medical Center authors, particularly that of Henry Silver who participates in 5 of its 40 chapters. Most of the 51 co-authors are members of the distinguished Department of Pediatrics of the Colorado Medical Center.

WILLIAM C. DEAMER, MD

* * *

THE CRITICALLY ILL CHILD—Diagnosis and Management—Edited by Clement A. Smith, MD. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1972. 276 pages, $11.75.

This volume is a compendium of articles which have appeared in series in *Pediatrics*. Each of the 22 chapters deals with a critical situation, often one which would reach the emergency room or which might be referred to a medical center. The authors are outstanding experts in their various fields and the book is edited by Clement Smith, Editor of *Pediatrics*.

Each subject is discussed in great depth and many portions are not easy reading. This is no Boy Scout Manual for the inept, but is designed for those with expertise and who have sophisticated equipment. Although, overall, the greatest value will be to hospitals with superior personnel, laboratory and other facilities, each chapter is loaded with valuable information and may be profitably read by any physician who might be confronted with these responsibilities. Although much of the material is complicated, the various authors have presented it well.

EDWARD B. SHAW, MD

* * *

VECTORCARDIOGRAPHY IN CONGENITAL HEART DSEASE—A Method for Estimating Severity—R. Curtis Ellison, MD, Associate in Cardiology, Children's Hospital Medical Center, Assistant Professor of Pediatrics at the Children's Hospital, Harvard Medical School, Boston; Norma J. Restieaux, MB, ChB, FRACP, MRCP (London), Senior Lecturer in Medicine and Cardiologist, University of Otago Medical School, New Zealand, formerly, Fellow in Cardiology, Children's Hospital Medical Center, Boston. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1972. 209 pages, with 138 illustrations, $13.50.

Many current methods of investigation of patients with congenital heart disease involve the use of complex techniques that not infrequently expose patients to discomfort and risk. The advantages of employing methods that are safe and reliable and may be used repeatedly even in seriously ill patients are obvious. One of the more important non-invasive techniques employed for the diagnosis and assessment of congenital cardiac disease is the vectorcardiogram. The current work is a summary of ten years of experience with the Frank vectorcardiogram at the Children's Hospital and Medical Center in Boston. Ellison and Restieaux have placed their patient material into fourteen categories, based upon the type of congenital lesion present. Emphasis has been placed upon using vectorcardiographic measurements to assess hemodynamic severity. They deal mainly with the left and right maximum spacial voltages and the orientation of these vectors in space.

The first four chapters of this text are devoted to technique. There is a general discussion of vectorcardiographic principles, lead placement, and the methods employed for the calculation of the maximum spacial voltages and orientation. Stress is placed on the simplicity of the technique and the fact that the work can be performed, in large part, by a technician. The advantage of adapting their technique to computer analysis is outlined clearly.

Specific cardiovascular malformations are discussed separately in the remainder of the text. The chapters devoted to vectorcardiographic correlations in aortic and pulmonic stenosis are especially worthwhile, since many correlations have been obtained between left ventricular systolic pressure and the leftward maximum spacial voltage in patients with valvular aortic stenosis, and between right ventricular systolic pressure and rightward maximum spacial voltage in pulmonic stenosis. Unfortunately, the vectorcardiographic assessment of residual obstruction has not been found to be helpful in patients who have undergone operation for their stenotic lesion. In this same regard, while the authors' analyses of data from groups of patients is extremely helpful, no correlations are put forth concerning the association in any individual patient of changing hemodynamics and changing vectorcardiographic findings. With regard to the many other congenital malformations discussed in this work, it would appear that the Frank vectorcardiogram is most useful in quantifying intracardiac pressure changes and substantially less helpful in supplying criteria for predicting the extent of derangements induced by volume loads.

The text summarizes the current state of the art. It is adequately illustrated and the figures are of high quality. This book will be an important addition to the library of the clinical electrophysiologist or the practitioner of pediatric cardiology.

WILLIAM F. FRIEDMAN, MD

* * *

TEXTBOOK OF ELECTROCARDIOGRAPHY—David Littmann, MD, Consultant in Cardiology, Formerly, Chief, Cardiology Section, Veterans Administration Hospital, West Roxbury, Massachusetts, Associate Clinical Professor of Medicine, Harvard Medical School, Lecturer in Medicine, Tufts University Medical School, Associate in Medicine, Massachusetts General Hospital, Boston, Senior Associate in Medicine, Peter Bent Brigham Hospital, Boston. Medical Department, Harper & Row, Publishers, Inc. 2350 Virginia Avenue, Hagerstown, Md. (21740), 1972. 533 pages with 627 illustrations, $22.50.

This first edition of a *Textbook of Electrocardiography* is divided into seven chapters devoted to the normal electrocardiogram, hypertrophy and enlargement, conduction disorders, coronary heart disease, miscellaneous conditions, the abnormal electrocardiogram of no characteristic pattern, and electrocardiographic interpretation, plus an electrocardiogram illustration index and a subject index. The book is primarily a compendium of the author's collection of normal and abnormal electrocardiograms accumulated over a 25-year period while teaching clinical electrocardiography to medical students and residents. The text is secondary to the illustrations, the vast majority of which are photographic recordings. The quality of the reproductions is excellent, and with rare exception they are well selected.

The text discussions are informative, well-stated and finely illustrated. However, that pertaining to left ventricular strain is confusing from the standpoint of attempting to differentiate the latter from ischemia or subendocardial infarction. The sections on ventricular hypertrophy are well-written, although the diagnosis of left ventricular hypertrophy with left bundle branch block is a controversial one. Other minor issues relate to the continuing usage of the confusing terms of peri-infarction and arborization or parietal block, the propriety of diagnosing left anterior hemiblock in the presence of left bundle branch block, and the omission of newer concepts of sequence of ventricular depolarization.

The author presents a sound discussion of coronary heart disease with classical references. In general his bibliography is well-selected in relation to basic material but lacks the newer references relating to hemiblock or to His bundle electrograms.

Arrhythmias and pediatric electrocardiography are minimally presented, but such was the intent of the author. With the exception of these two drawbacks, this book represents a pracical, inclusive, and well-organized atlas of electrocardiography with excellent tracings and informative discussion in sufficient detail of most of the basic problems encountered in clinical electrocardiography. Dr. Littmann's approach is a classic and wise one which should prove most helpful for the medical student and young physician, but also will serve a useful purpose for the internist and cardiologist. However, it would be hoped that in the next edition the newer concepts pertaining to His bundle electrograms and A-V conduction would be included.

HILLIARD J. KATZ, MD

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CURRENT PSYCHIATRIC THERAPIES—An Annual Publication—Volume II—1971—Edited by Jules H. Masserman, MD, Professor of Psychiatry and Neurology, Northwestern University, Chicago. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1971. 224 pages, $14.00.

This eleventh volume of *Current Psychiatric Therapies* fulfills the same functions as its predecessors: it presents a number (27) of brief articles, each of which deals with a new or reconsidered approach to psychiatric problems. None of the articles is sufficient to describe the approach in detail; each can serve to alert the reader to the existence of the approach and suggest readings to develop a wider understanding. The book, then, is of heuristic, rather than substantive, value, and it succeeds in this aim. The articles are of generally good quality, especially those of Colby on Computers in Treatment of Autistic Children, Catanzaro on Telephone Therapy, Horowitz on Art Therapy, Hollender on Marital Therapy, Mathis on Group Therapy for Exhibitionists, and Seeman on Multimodal Group Therapy, and Felder on Partial Hospitalization. The price of $14.00 is excessive.

C. PETER ROSENBAUM, MD

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URINARY TRACT INFECTION AND ITS MANAGEMENT—Edited by Donald Kaye, MD, Professor and Chairman, Department of Medicine, The Medical College of Pennsylvania, Philadelphia. The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Mo. (63141), 1972. 290 pages, $22.50.

This relatively slim volume contains a great deal of well-organized and clearly presented information and advice relating to this very challenging problem. There are thirteen authors who individually and collectively contribute the best current knowledge of the classification, pathogenesis, diagnosis and management of urinary tract infection. The well-defined and succinctly written chapters are competently edited by Donald Kaye who in addition contributes some of the most important material.

The reviewer has been most favorably impressed by the thoroughness with which the newer diagnostic procedures and therapeutic attitudes are presented. The immunological aspects of urinary tract response are given due consideration. There is also some mention of the recent and continuing very exciting work by Fair and Stamey on the immune substance found in the prostate. The difficult challenge of asymptomatic bacteriuria is gone into and the importance of this problem is evaluated in relation to age and other factors.

This work represents the approach and attitudes of non-surgeons with the sole exception of the chapter by John McGovern. He discusses the question of "surgery in the management of patients with urinary tract infections." However he directs most of his attention to this problem in children. Perhaps he felt that obstructive infectious urinary problems in the adult would demand a urological consultation, and discussion here would be redundant. It is the opinion of this reviewer that some further emphasis on the importance of the female urethra in relation to recurrent infection might be distinctly valuable. Beyond this one point there would seem to be very little room for criticism.

This volume is highly recommended for the internist and general practitioner and the urologist as well. It might well be a "must" for the medical student.

THOMAS F. CONROY, MD

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GENERAL UROLOGY—Seventh Edition—Donald R. Smith, MD, Professor of Urology and Chairman of the Division of Urology, University of California, San Francisco, Consulting Urologist, San Francisco General Hospital, Consulting Surgeon (Urology), Veterans Administration Hospital, San Francisco. Lange Medical Publications, Drawer L, Los Altos, Ca. (94022), 1972. 436 pages, $8.50.

Dr. Donald Smith, Professor of Urology at the University of California, San Francisco, has "done it again." The seventh edition of his classic paperback, *General Urology* is a gem and a *must* for all medical students and urological residents. At the beginning of the year with each new group of medical students, I always tell them Smith's book is their "Bible," and that if they know everything that is in it, they will know a great deal more than most urologists do.

In 31 carefully written chapters he covers the entire field of clinical urology. The organization is excellent; and as usual, the index and the references are clear and up-to-date. The new section on Radioisotopic Kidney Studies by Powell and Weiss is a valuable addition.

The illustrations, in clearly understood black-and-white line drawings, are excellent; and the reproduction of x-ray films is superior for a book of this sort. The fact that this text has been translated into Spanish and German, and is now being edited for French, Greek, Portuguese and Polish editions, speaks for its usefulness. It is a great and useful handbook of general urology.

WILLARD E. GOODWIN, MD

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PEDIATRICS—Fifteenth Edition—Editor: Henry L. Barnett, MD, Professor and Chairman, Department of Pediatrics, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York; Co-Editor: Arnold H. Einhorn, MD, Professor of Pediatrics, Albert Einstein College of Medicine of Yeshiva University, Deputy Director of Pediatrics, Bronx Municipal Hospital Center, Bronx, Visiting Professor of Pediatrics, University Children's Hospital, University of Bern, Switzerland. Appleton-Century-Crofts, Educational Division, Meredith Corporation, 440 Park Avenue South, New York City (10016), 1972. 2,070 pages, $26.50.

This represents the 15th Edition of Holt's *Diseases of Infancy and Childhood,* a complete and authoritative textbook of pediatrics which originally appeared in 1896. The editors have been joined by an increasing number of contributors with each edition, and more than 200 authorities have participated in the preparation of this volume. This reflects the increasing complexity and subspecialization within pediatrics, and the effort of the editors to seek those well qualified to prepare different sections.

The sections and chapters reflecting changing patterns of care or increasing emphasis include the community aspects of pediatric practice, the epidemiology of accidents and congenital malformations and a detailed section on perinatal medicine. A number of the weaknesses evident in earlier editions have been corrected, and skillful editing has removed the irregularities often seen in a book written by numerous individuals.

This book should be a part of every hospital and medical library and can be regarded as an authoritative and useful reference source for the practicing physician who deals with the problems of the child and the adolescent.

Paul F. Wehrle, MD

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CARDIAC SURGERY (Second Edition)—Edited by John C. Norman, MD, Appleton-Century-Crofts, Educational Division, Meridith Corporation, 440 Park Avenue South, New York, N.Y. (10016), 1972. 703 pages, $18.95.

Everybody likes Jack Norman. He is bright, attractive, and altogether charming. Nevertheless, he has never really been "into cardiac surgery." Perhaps for that reason it is an anomaly that he has edited a book on cardiac surgery, now in its second edition. It could be stated that this is a book on cardiac surgery written by too many non-cardiac surgeons. For example, a chapter on the immunologic basis of cardiac homograft rejection was written by three men who have no experience at all in cardiac transplantation. Still, the chapter is 38 pages in length, three times longer than Dick Lower's concise statement in the preceding chapter on cardiac transplantation. An obsolete chapter on hyperbaric oxygenation remains in the book; certainly this could be deleted from the next edition. George Clowes has a book within a book, the physiologic basis of cardiac surgery. Not very interestitng.

All-in-all, this is a compendium of 34 articles by 50+ authors covering many aspects of cardiac surgery. It seems to offer little additional information to that available in other books on cardiovascular surgery.

Norman E. Shumway, MD

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ATLAS OF NUCLEAR MEDICINE—Volume 3—Reticuloendothelial System, Liver, Spleen and Thyroid—Frank H. DeLand, MD, Professor of Radiology, Department of Radiology, University of Florida College of Medicine, Gainesville; Formerly, Associate Professor of Radiology and Radiological Science, Johns Hopkins Medical Institutions; Henry N. Wagner, Jr., MD, Professor of Medicine, Radiology and Radiologic Science, Johns Hopkins Medical Institutions. W. B. Saunders Company, West Washington Square, Philadephia (19105), 1972. 292 pages with 196 illustrations, $21.

Volume III of the *Atlas of Nuclear Medicine,* covering the reticuloendothelial system, liver, spleen and thyroid is a lucid presentation of selected cases to illustrate the value of tracer procedures in the evaluation of diseases of these organ systems.

In this volume, as in previous volumes, there are superb introductory sections stating the criteria for interpretation and technical features which should be used when these studies are performed. In addition to the excellent scans, there are coordinated anatomic drawings, good reproductions of radiographs and concise case histories. The advantage of interpreting scans, in light of all other patient data is clearly presented.

The Atlas is divided into four sections, each covering one area. Unfortunately, the first section presented on the reticuloendothelial marrow, is the least proven of all areas, and the least convincing.

The sections on liver and spleen are presented clearly, with many examples of the more common abnormalities and their unusual variants. The limited value of the liver studies in patients with parenchymal liver disease is not clearly stated in the text. However, the discussions on jaundice, dilated bile ducts and cysts, abscesses, hepatic regeneration, hematoma and anatomous variants are excellent. In addition, examples of the value of ionic gallium and hepatic tomography are also presented.

The section on thyroid clearly presents the advantages of using the pinhole collimator and technetium for thyroid evaluation. The enormous range of appearance of the normal thyroid as well as the appearance in disease states is clearly presented. The case presentations illustrate the value of a full thyroid profile consisting of the scan, uptake, T3 and T4 to arrive at a correct diagnosis in patients with thyroid disease.

The information presented in this volume of the Atlas will be very helpful to practitioners, students and technologists in the field of nuclear medicine. The quality of the images, and techniques suggested for obtaining them, speak for themselves. Particularly impressive is the wide range of normal which is presented. This Atlas will serve as reference work for many years to come.

Florian W. Zielinski, PH D

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THE PRINCIPLES AND PRACTICE OF MEDICINE—Eighteenth Edition—Edited by A. McGehee Harvey, MD, D SC (Hon.), Professor of Medicine and Director of the Department of Medicine, Physician-in-Chief, The Johns Hopkins Hospital; Richard J. Johns, MD, Professor of Medicine, Massey Professor of Biomedical Engineering and Director of the Department of Biomedical Engineering; Albert H. Owens, Jr., MD, Professor of Medicine; Richard S. Ross, MD, Professor of Medicine, Susan and William Clayton Professor of Cardiovascular Disease; all from The Johns Hopkins University School of Medicine. Appleton-Century Crofts, Educational Division, Meredith Corporation, 440 Park Ave. So., New York City (10016), 1972. 1650 pages. $24.50.

Although the present volume purports to be the eighteenth edition and continuation of Osler's famous "Principles and Practice of Medicine" it is in fact the second edition of a work with entirely new directions, both in form and in spirit, from those of its distinguished predecessor. As mentioned in a review of the earlier volume in California Medicine [112:102-103, April, 1970], it fulfills Osler's hope as expressed in the seventh edition that it would become a Johns Hopkins textbook of medicine but only in the sense that its contributors are drawn exclusively from present and some past members of the faculty of that institution. It differs in that it is intended to serve as a text complementary to the many existing comprehensive textbooks of medicine and consequently, "emphasizes clinical problems rather than disease entities" and is said euphemistically to be patient-oriented rather than disease-oriented.

The new edition has increased in bulk by some 178 pages, exclusive of index, but the page count is deceptive since there has been a considerable saving of space for additional material by a sharp reduction in the size of the illustrative and tabulated figures. However, the increase in size is somewhat illusory since it does not differ very appreciably from that published in 1968 and previously reviewed. The number of sections remains the same although there has been some rearrangement of the sections and there are minor changes in the constituent chapters. The section which has undergone the most extensive revision is that on endocrinology, but even that, although showing an improved approach based upon concepts of hormonal "feed-back," contains little substantive change.

The text commonly opens with a review of basic physiological and biochemical information in its application to the solution of clinical problems; that is, what used to be called applied physiology and biochemistry. This basic preliminary information too frequently leaves much to be desired. Thus, the introductory material to the chapter on metabolic bone diseases contains so many inaccurate statements as to be unacceptable. For example, what are we to say of such elementary errors that "The development of the long bone is through both endochondral and intramembranous bone formation"; that the osteon is "the unit of the former (compact bone), the trabecula of the latter (cancellous bone)," contrary to the experimental evidence of Benninghoff and others; that the "physis" is "also known as the epiphyseal growth plate" which is the use of a term not accepted in scientific nomenclature and further is the improper use of an inapplicable abstract-noun as if the authors of the Hippocratic Corpus who introduced the cognate terms, epiphysis, apophysis, etc., did not know the niceties of their own language. However, it would be invidious to draw attention to more of the errors or ambiguities in the sections on basic science, but with the talent in the basic sciences available at Hopkins they should be minimal and to avoid dogma more attention given to the controversial.

The symptomology, clinical manifestations, laboratory tests, differential diagnosis and other pertinent information are summarized in a series of tables which are supported by the textual discussion presenting thumbnail sketches of the various disease entities, their management, and therapy. An important feature are the chapters on special problems such as those on fevers of obscure or unknown origin, deficiencies of immunity, iatrogenic conditions and the like.

The essential difficulty of a text built upon the concepts outlined in the preface is the question of consistency. Sooner or later the clinical entity as such obtrudes itself to a greater or lesser extent as a conventional description, or rather a thumbnail sketch, of disease which is of doubtful pedagogic value so that the emphasis falls on laboratory diagnosis rather than on clinical diagnosis backed by the laboratory. After all, despite the dictum that the text is patient-oriented rather than disease-oriented, generally, like Einstein's statement, "Energy has mass and mass represents energy," there is no disease without the patient. Nevertheless, the presence of a new edition so soon after the last suggests that the text fulfills a need and is popular.

John B. deC. M. Saunders, MD

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PROGRESS IN MEDICAL GENETICS—Volume Eight—Edited by Arthur G. Steinberg, PhD, Professor of Biology, Department of Biology, and Professor of Human Genetics, Department of Reproductive Biology, Case Western Reserve University, Cleveland; and Alexander G. Bearn, MD, Professor and Chairman of the Department of Medicine, Cornell University Medical College, and Physician-in-Chief, The New York Hospital, New York City. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1972. 319 pages, $19.50.

As the editors note, the topics covered in this eighth volume of an annual series illustrate the diversity of subjects which are of interest to medical geneticists. Compared to earlier volumes, the present contains a greater proportion of articles which may be of only peripheral interest to clinicians. The first of the seven chapters is by Fenner and covers the genetics of animal viruses and the host's responses to them. While there have been many excellent review articles on the genetics of viruses, this is one of the few restricted to animal viruses. The discussion considers the following groups of human viruses: adenovirus, poxvirus, picornavirus (polio, common cold, etc.), togavirus (encephalitis, yellow fever), myxovirus (influenza), and paramyxovirus (mumps, measles). In the next chapter German reviews the role of chromosome changes, particularly chromosome instability, in relation to neoplasia, including an evaluation of Bloom's syndrome, Fanconi's anemia, ataxia telangiectasia, and xeroderma pigmentosum. He concludes that the relationship of chromosome changes to neoplasia is not clear at the present time, but that future consideration requires an open mind so that potential significant relationships will not be overlooked. In the third chapter Morton considers the future of human population genetics and concludes that the role of mathematics in human genetics will increase in areas such as the relationship of genotypes and phenotypes, estimation and tests of hypotheses, segregation analyses, evaluation of relationships and proportion of genes in common among related individuals, genetic population structure and genetic polymorphisms. Kirkman summarizes our current understanding of genetic aspects of human enzyme defects and emphasizes the following areas: genetic heterogeneity; partial (incomplete) defects in which some enzyme activity remains; mechanisms of enzyme deficiencies, including production of an abnormal protein without enzyme activity versus reduced production of a normal enzyme; potential treatment of enzyme defects; heterozygote detection; problems in enzyme analysis for diagnosis; and molecular mechanisms of dominant disorders. Clarke summarizes the history and world experience in the prevention of Rh immunization which represents one of the major breakthroughs in management of a disorder with a genetic basis. In a short summary, Brady and Kolodny review the rapid recent progress towards a clearer understanding of the disorders of ganglioside metabolism. Finally, Scott reviews the genetics of short stature and emphasizes the genetic heterogeneity which can account for short stature. He includes the nomenclature for constitutional disorders of bone which was proposed in 1970. The volume contains a useful index and each of the articles contains a good bibliography. Since each of the articles is by an expert in the field, the topics are critically reviewed and summarized, making them a useful source for current information on the topics covered.

Robert S. Sparkes, MD

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PEDIATRIC ORTHOPEDICS—Volumes I and II—Mihran O. Tachdjian, MS, MD, Head, Division of Orthopedics, Children's Memorial Hospital, Chicago, Illinois; Professor of Orthopedic Surgery, Northwestern University Medical School, Chicago, Illinois. W. B. Saunders Company, Publisher, West Washington Square, Philadelphia, Pa. (19105), 1972. 766 pages, Volume I, 1,001 pages Volume II, $65.00.

Pediatric Orthopedics by Mihran Tachdjian is a two-volume monumental work covering the subject. The first volume is 766 pages long including the list of references. The second volume brings the total work to 1,767 pages. The work is beautifully organized, it contains all the fundamentals which are explained in an extremely readable, simple form. The photographs are accurate and typical of the conditions presented. The diagrammatic illustrations are outstanding and present concisely and succinctly some of the complicated syndromes seen in bone diseases of a clinical nature, as well as many of the operative procedures. At least one important operative procedure for every surgical condition is presented in detail.

Where there are several operative procedures available, most of the important ones are briefly described so that a broad picture of the available surgical treatment is available.

There are several other works by outstanding authors in pediatric orthopedics but none measure up to this monumental contribution by a well recognized authority on the subject. The two volumes are a must for any orthopedist who does a good deal of children's orthopedics; they are certainly a must for any medical library with a teaching program in children's orthopedics.

R. Kirklin Ashley, MD

California Medicine
THE WESTERN JOURNAL OF MEDICINE

A New Journal and An Energetic Medical Association

With the beginning of the year 1974, the journal that the California Medical Association long has proudly published under the banner California Medicine spreads into wider fields as a regional journal to be called The Western Journal of Medicine.

Ever since Dwight L. Wilbur pointed California Medicine in that direction six years ago when he resigned as editor to become president of the American Medical Association, the editor and the associate editor who succeeded Dr. Wilbur have been deliberately preparing the journal for a bigger and more influential part in medical journalism. In each issue they sought to offer a balanced fare of scientific and social progress—material for students, scholars, practitioners, academicians, researchers and even politicians—through original articles, editorials, and features of interest not only to Californians but to readers throughout the nation.

Now, after six years of stewardship, the present editors of California Medicine, with the blessings of the CMA Council, have undertaken to expand the magazine's circulation to include Oregon, Washington, Idaho and Alaska. With this expansion, the Council agreed to draw upon the research and medical accomplishments in these states as well as in California, to appoint members of the Editorial Board from the areas to be served, and to solicit articles there as well. In addition, the Council voted to ask the state medical associations in the Northwest to recommend The Western Journal of Medicine to their members and to supply listings for the monthly catalog of continuing medical education opportunities that are printed in the journal.

As an earnest expression of its readiness to trade a forgivable provincialism for the greater opportunity of sharing and further improving a journal in which we have taken increasing pride, the Council relinquished the name California Medicine and took aim on the future with The Western Journal of Medicine.

In this farewell issue, California Medicine focuses its attention on the progress and accomplishments of the California Medical Association—its role in science and politics, society and the economy; its position on important medical and health subjects; its progress—highlights of the past, challenges of today, and aims and goals of the future.

E. Kash Rose, MD
Chairman of the Council
California Medical Association

Enlightened Self-Interest

This Special Report on the California Medical Association is intended to show how the CMA serves the interests of its members with a sophistication and an effectiveness which appear to be quite unique among professional associations.

Some time ago it became obvious enough that many if not most of the customary ways professional associations sought to serve the interests of their members were not working very well, particularly in the public arena. In some instances these efforts were indeed actually counterproductive. This seemed particularly true of professional associations in medicine. To put it bluntly, the self-interest of physicians could no longer be pitted against the self-interest of society with either success or impunity. New approaches and new techniques were clearly and urgently needed.

The CMA responded to this challenge and has pioneered many new approaches and new techniques to make a professional association more effective in today's society, and furthermore they seem to be working. CMA is finding scientific, highly professional and enlightened ways to better serve its members, their profession and the public. The scope and effectiveness of these activities should be more widely known.

In this final issue of California Medicine before it becomes The Western Journal of Medicine, the editors present this Special Report on the California Medical Association and salute the CMA for what it is doing in the enlightened self-interest of the physicians of California, their patients and the people of this state. They also applaud the growing influence that this association is having on the national scene.

Refer to: Watts MSM: The threads of a professional association through the fabric of society—The CMA as a new kind of organizational instrument. Calif Med 119:3-17, Dec 1973

The Threads of a Professional Association Through the Fabric of Society

The CMA as a New Kind of Organizational Instrument

MALCOLM S. M. WATTS, MD, *San Francisco*

*"A profession has for its prime object the service it can render to humanity."**

THE STATEMENT above applies as much or more to medicine than to any other profession. Throughout the centuries this has generally been the goal of medicine and during this century there is no reason to believe it has swayed from this objective. However, during the past decade or two the medical profession has been under almost unprecedented attack at a time when it was achieving unprecedented success in service to humanity. And in California, as everywhere else, the profession has been taking its lumps.

For many years the California Medical Association's leadership groped to find an appropriate role for CMA and for organized medicine, which found themselves so much on the defensive, as the new goals and values in the new national purpose in health care began to take shape. In retrospect it now appears that a statement adopted by the Council on 7 August 1965 set the stage for much that CMA has done since that time, although the statement itself was limited to the "Medicare" law (PL 89-97, Titles XVIII and XIX of the Social Security Act) and its regulations. The Council said:

> ". . . that the CMA consider diligently the impact of Public Law 89-97 on patient care in coming months and years; and when regulations are imposed which are not in keeping with sound medical practice, the Association will forcefully pursue corrective action, through regulatory changes and/or legislative modifications."

In 1967 a fiscal crisis developed in California "Medi-Cal" program (Title XIX of the Social Security Act) and the Council then found it necessary to adopt a "Statement of Principles on Medi-Cal" in order to implement its policy to "forcefully pursue corrective action." This CMA statement utilized the expertise and experience of

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*Leake CD (Ed): Percival's Medical Ethics. Baltimore, Williams and Wilkins Co., 1927, p 257.

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medicine to give strong support to the aims of the program and to its beleaguered scientific and humanitarian values, and to criticize constructively the economic allegations against the program. Subsequently there have been many other and considerably more forceful measures taken to "pursue corrective action" in this program. In a very real sense this was professional service rendered to humanity and in a very real sense it marked the beginning of new and far reaching activities of the CMA in behalf of better medical care and better health for the people of California.

It is the thesis of this discussion that during the past decade the CMA has begun to develop as an increasingly effective social organizational instrument which is no longer merely an association to satisfy the needs of its member physicians, but rather has become their instrument for bringing the knowledge and influence of the profession effectively to bear to serve humanity in what has become the enormously complex and highly interdependent social, economic and political system of today's society. To accomplish this, CMA has begun to develop new insights, new technology and new organizational approaches for more effective action for the association and its members. It is beginning to study modern society and its ills as a physician studies his patient; and as it does so it is beginning to understand more about the nature of modern society and how medicine through its professional association can be more effective as one of the principal threads in the fabric of that society. In the process CMA has become in many ways a new kind of societal organization for which there is no previous model. If this is in fact the case, there are important implications for all of organized medicine and indeed for society as a whole.

This paper will begin with a brief and entirely superficial discussion of the causes and impact of increasing interdependence in what has always been a more or less independent medicine and society, some of the problems this has brought to both, and the failure of both so far to adapt effectively so as to meet these new problems. It will then assess medicine's responsibilities and strengths and show how the thread of medicine weaves through the fabric of society. This will be followed by an analysis of the means CMA appears now to be using to strengthen the thread of medicine and to weave it more closely through fabric. Finally there will be a few suggestions of possibilities for future development by CMA, as it pioneers the role by which such an organization can achieve professional, social, economic and political effectiveness and develop the means by which this can be done.

Interdependence—A Key Reality in Medicine and Society

A key reality of the modern age is a growing technologic and human interdependence, and a key unsolved problem of both medicine and society is how to deal with it. The evidence of not coping with the problem abounds everywhere and it is the genius of the CMA that organizationally it has in fact begun to cope realistically and on a scale which is beginning to be effective, as will be shown later in this report.

The causes of the growing complexity and interdependence within and between medicine and society are obvious enough. There is more medical science, there is more technology in both medicine and society, and there are more people both in the health care professions and in the population as a whole. As science and technology become more complex, specialization becomes inevitable, and the other side of this coin is inevitable interdependence among the specialists. Technology also becomes interdependent with technology as it becomes more complex—as becomes evident, for example, when there are area-wide electrical blackouts. And as the numbers of people increase in the population as a whole so does their dependence upon one another, and thus their interdependence. More, the reality of the closed biosphere will soon add new dimensions to the scientific, technical and human interdependence of both medicine and society as new and as yet dimly perceived ecological dependencies and interdependencies become recognized as essential to assuring biological well-being and even survival. All of this is occurring now and it can only increase. In a very real sense, and unavoidably, interdependence is slowly subsuming independence, and ways have yet to be found to cope with the fact of interdependence itself and yet satisfy the human need and desire for personal independence and personal fulfillment.

The signs of failure to cope or to adapt are everywhere.

To begin with, *science* has so far failed to find effective answers for these problems of human and technologic interdependence. There is neither the knowledge nor the technology to deal scientifically with how human nature can or should cope with the new technologic, social, economic and political interdependencies which have come into being as a result first of the industrial revolution and, more recently, of the scientific revolution which has only just begun to get under way. And it seems likely that this will remain so until such time as the behavioral sciences, social science, the science of economics and political science find or develop stronger roots in human nature and human biology. After all, it is his human and biological nature which determines man's behavior and even his needs, and it is this which must become basic to social, economic and political science before these sciences are likely to contribute much to finding scientific solutions for the problems of growing interdependence. In any case, experience so far suggests that current social, economic or political theory has not found very satisfactory or lasting solutions to the problems of human interdependence. In fact, if anything, the reverse seems to be true—that efforts, even massive ones, to put current theories into practice have too often foundered or failed and frequently ended by compounding the problems they were expected to solve.

Turning to *technology* itself, the machines and computers which man has created to do his work and to help him solve his problems have in themselves created serious and sometimes enormous problems. Beyond their extensive interdependencies with regard to the energy or the fuel necessary to operate them, or the technology necessary for their repair or maintenance, there is growing evidence to suggest that they are beginning at times to make mockery of man's independence by making him so dependent on them that they seem to be developing the capability to control, to thwart or even to destroy him. The growing interdependencies between men and machines are not to be taken lightly.

In *society* there are signs of cracking and crumbling which are to be clearly seen in many of the important human institutions which hold society together. Not only medicine, but the law, the churches, the educational system and even the military and the police have all had a share of trial and tribulation. And at this writing even the federal government seems to be coming apart at the seams. Each day brings further indications of failure to cope with the issues of human independence and human rights on the one hand, and the imperfectly understood issues of human interdependence and human behavior at home and abroad on the other. The entire societal picture suggests a broad scale failure to cope.

As for medicine, very great technical success during the last half century has paradoxically contributed greatly to these problems of both medicine and society. Yet the profession has hardly considered at all the impact of this accomplishment or the problems it has created. There is fractionation of the science and technology among the specialties and disagreement within the organized profession concerning what should be done about social, economic and political issues. And there has been a notable lack of real teamwork among health professionals or within the health care industry for problem solving or coordinated action—although there is some recent evidence that a beginning is being made.

This, then, is something of the background for many of the unsolved problems of today's interdependent society, and this is the milieu in which the medical profession must begin to function and perform effectively if it is to achieve Percival's prime object of a profession—"the service it can render to humanity." It is against this background and in this milieu that CMA appears to have begun to develop a new kind of organizational instrument which shows real promise of becoming an effective means for the medical profession in California to cope with the problems it must deal with if it is realistically to serve the people of this state.

Medicine as the Scapegoat—The CMA Response

The broad scale failure to cope just described developed gradually, but the tempo increased considerably in the 1960's and 1970's when it became apparent to many that some of the basic social institutions were simply not working and that the professions (including medicine) were not providing satisfactory answers to the new problems of technological and human interdependence as fast as these were being created in their fields by the industrial and scientific revolutions. The evidence for this is substantial. There have been upheavals in the churches, in the schools and colleges, unprecedented disruptions in the military, and an all too evident failure of the legal system to function either quickly or effectively, and at times even with justice. And as previously noted the social and economic theories of the day simply did not solve the social and economic problems when they were applied in practice, and whatever the politicians did seemed to do all too little to improve the situation and often appeared to worsen it.

In retrospect there is much to suggest that an attempt was made to make medicine a scapegoat and to pin much of the blame for societal difficulties on the medical profession and its presumed failure to provide adequate health care for each and every citizen. In any case, and for whatever reason, the medical profession, which had made enormous scientific advances with generous public support in the previous two decades, was suddenly held responsible for all the real and imagined poor health in the nation. There were public attacks upon the profession by social theorists, economic theorists and politicians, many of whom seemed happy enough to direct attention away from the social, economic and political problems they could not solve. They were joined by the press and the communications media, which often seemed to fan the flames. Medicine, elitist by tradition and by necessity, seemed fair game in an era of egalitarian consumerism. The medical profession was attacked as greedy, self-serving and presumably responsible for all the ill health which was claimed by some to be the main cause of poverty itself. Medicine was blamed for the maldistribution of health care personnel and services and for the rising costs of medical care, which were ascribed almost entirely to doctor's fees. It was accused, because of self-interest, of politically obstructing any and all efforts by government or others to improve the situation, even though experience had shown and continues to show that most such efforts to date have done little but add substantially to the cost and complexity of health care with comparatively little overall improvement.

However, these attacks did not destroy the medical profession or even its good name, but rather have served to strengthen it. Patients continue to believe their doctors are honest and serving them well. Medical progress continues to impress the public, the interest of young people in becoming physicians has steadily increased and is now shattering all previous records, and the profession itself still rates very high indeed in any public opinion polls where such things as trust and competence are at issue.

But the physicians of California, like physicians everywhere, were ired by these attacks and allegations, and the membership of the CMA demanded that something be done. At first the emphasis was on protest and rebuttal and then on an intensified public relations effort. But soon there developed an awareness that organized medicine often did not have the knowledge or the data base to refute or rebut successfully, nor did the profession have any authoritative understanding of just what the social, economic and political problems were that it was being castigated for not solving, or of what should be done about them by the profession or anyone else. It gradually became obvious that the association would need to develop new dimensions of organizational activity if it were to do much more than protest. There never was any formal action taken or any formal policy enunciated, but rather there was a tacit consensus at almost a subconscious level that there be a reassessment of organizational approaches by CMA, that an adequate knowledge and data base be developed, and that an effective technology for action and advocacy be developed.

There was no good organizational model to copy. The association found itself embarked upon what now appears to have been a pioneering effort by a professional association to adapt its purpose, its structure and its function so as to improve "the service it can render to humanity" within the scientific, social, economic and political framework of modern society. Slowly and without fanfare, CMA began to develop a model of an entirely new kind of professional organizational instrument which is now showing increasingly effective performance not only within the framework of today's society in California but within the framework of organized medicine as well. Not surprisingly, the approach has been "clinical"—that is, quite similar to the way a physician approaches a difficult problem with a patient where he is working against time with poor data, or when so little is actually known about the condition that it is not yet really diagnosable or treatable scientifically in the present state of knowledge. His cardinal rules in such situations are to do what seems best for the patient with what knowledge and data are available, try to add to the knowledge and data, and above all to do no harm.

This has been the approach of CMA to this new and challenging problem.

Assessing Medicine's Responsibilities, Strengths and Functions

In order to understand the professional role CMA is developing for this professional association in today's society it is necessary to appreciate some of the fundamental responsibilities and strengths of medicine in this or any society. These may be thought of somewhat as follows:

The Responsibilities

It has been said that the fundamental act in medical care is the assumption of responsibility for the welfare of a patient. This is accomplished when a patient agrees to place himself in the care of a physician and the physician agrees to accept responsibility for the care of the patient. This is the foundation for the much discussed doctor-patient relationship and is the basis for both the responsibilities and the strengths of the medical profession. Within this relationship the physician seeks to work with the patient to strengthen what is weak and to repair what is defective and thus to restore, improve, or maintain his health. This basic focus is on and with the patient. But the physician's responsibility for the care of his patient and his capability to render this care can no longer be separated from the capabilities, limitations, complications and restrictions of medical practice and the delivery of health care in today's society. These all must be taken into account by today's doctor taking care of today's patient. This being the case, medicine inevitably becomes more and more involved in the broader aspects of health care delivery and in the problems of modern society as they pertain to health and health care. And there is some good reason to believe that this involvement will of necessity extend to, and in time cause the medical profession to develop an interest in, the health and welfare of society—that is, the population as a whole and the human institutions within it—which will be quite comparable to the interest it now has in the individual patient.

Some of medicine's responsibilities and involvement with respect to society as a whole are already becoming evident. They are rooted in the profession's unequaled and authoritative knowledge of medical science and of what is involved in the care of patients. Hence medicine becomes society's authority on health and its disorders, and it becomes society's professional custodian of this knowledge with the primary responsibility for disseminating it, applying it in practice and adding to it. The dimensions of this responsibility now clearly extend beyond medical science and the care of the sick. They have begun to reach into health care delivery, and into many social, economic, political, environmental and ecological aspects of health and health care, although in these fields the responsibility is fortunately shared with many others. What the future holds with regard to this responsibility is not so clear, but as the industrial and scientific revolutions progress, the problems of human and technological interdependence are certain to compound, and it seems inevitable that medicine's understanding of health and its disorders will achieve new dimensions. As this occurs there will be new professional responsibilities which will develop and extend even further the broader professional role which CMA has begun to develop for this association.

The Strengths

The strengths upon which CMA is building its new professional role are many. As has been said, they are rooted in the doctor-patient relationship, a relationship that can be fully as strong as that with priest, protector, teacher, or legal advisor. This fundamental strength has yet to be fully brought to bear in the association's new professional role. Another base of strength is a proven record of superbly applying medical science in daily patient care; and there is a strong public identification of the profession with helping people and of applying science and skill to relieve suffering, to improve health and even to enhance the quality of life.

A very important strength which has only just begun to be put to practical use even by CMA is the fact that medicine is the only segment of society that can truly represent the real consumer of health care, that is, patients. Most of those who are identified as "consumers," and the public and even legislators, are usually quite healthy and seldom have had direct contact over any length of time with any broad spectrum of patients. Practicing physicians, as a life work, do have direct contact with the spectrum of disease and the real problems of their patients. Physicians therefore are in strong position to speak for the afflicted, even though whenever they do so they are sure to be accused of speaking only for themselves as providers. Fortunately, there is here no basic conflict for the physician, since what is best for patients is in the long run always best for the doctors.

A final and most important strength lies in the fact that the ramifications of medicine and the medical profession extend throughout the whole fabric or framework of modern society and touch closely upon many aspects of science and technology, human nature and human behavior, and many social, economic, political and legal problems as these affect human health and well-being.

These are some of the strengths of medicine in modern society which CMA is seeking to develop and apply as it undertakes to expand the organizational role of medicine to help solve some of the pressing problems of health and well-being in today's increasingly interdependent yet still independent society.

The Professional Functions

The CMA Committee on the Role of Medicine in Society, whose series of reports has been drawn upon heavily in the preparation of this discussion, addressed many of these problems of responsibilities and strengths of medicine. On its Sixth Progress Report* the committee undertook the essential task of identifying and defining the professional functions or tasks which physicians and only physicians can perform. This question is more easily asked than answered but the committee believed that it identified three essential functions which, taken together, define what the physician does throughout the spectrum of health care and therefore describe his professional role in modern society. These three essential functions are as follows:

1. The physician gives a professional opinion or judgment based upon his knowledge, experience and expertise with respect to health and its derangements.
2. The physician is an essential participant in all the decision-making processes throughout the whole spectrum of health care because of knowledge of health and its derangements, and of health care.
3. The physician performs certain professional procedures and services in health care, and plays certain roles for which he must have practice skills.

As noted by the committee, each of these functions derives from the physician's knowledge of the subject matter of medicine and his professional competence in patient care. This professional knowledge and professional judgment make it essential that physicians participate whereever important decisions are made with respect to health and health care, whether these be in medical practice or elsewhere in society. Where this is not done, experience has shown that costly mistakes are more apt to be made than might otherwise be the case. Involvement of physicians in all important decision making in health care is a new concept. It appears to be valid and it should be done more widely. While rendering opinions and participating in decisions are essential functions, they are not all, nor are they enough. They require that physicians possess and use skills as problem solver, manager, highly skilled technician, teacher or advisor and advocate if the medical profession is to perform effectively in today's society.

Thus the professional responsibility of medicine begins with responsibility to the patient, but this cannot be separated from health care within the framework of today's society and it quickly becomes clear that medicine has professional responsibilities to society itself. There are also fundamental strengths upon which medicine and only medicine can draw. The essential functions of the physician, as these are identified and described in the previously mentioned report of the CMA Committee on the Role of Medicine in Society, offer a conceptualization within which physicians and the medical profession can begin to mobilize and apply their very considerable strengths to carry out their responsibilities for the betterment of health care in modern society. As will be seen, the California Medical Association has achieved some awareness of the scope and magnitude of medicine's role and is beginning to develop a new kind of network of professional activities for the association within the fabric of today's society.

The Thread of Medicine in the Fabric of Society

The thread of medicine runs through the whole of the fabric of society, particularly today's society. Indeed medicine may be one of the strongest of many threads that, woven together, are what holds society together. Among the more easily identified strands is some system of beliefs, with values and a code of morality or ethics. This system of beliefs may find expression in a religion and some kind of priesthood. Another thread is the requirement of protection from violence or attack whether from without or within. Therefore, there is some kind of military or police. The human interaction and exchange which is characteristic of any society requires some rules of order, and thus there are laws and some means of law enforcement. Then there is need for some means for the collection, storage and transmission of knowledge and experience, and so there are systems of education and communication. Finally there is a need for society to be healthy and also to be able to do something about ill health, and that need must be met in some kind of science or system of medicine and some kind of physician or medicine man. It is noteworthy that each of these threads has attached to it a key and generally honored professional—the priest, the soldier or police officer, the attorney or judge, the teacher or scholar, and the physician or medicine man.

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*The physician and his practice: 1980-2000—Sixth Progress Report of the CMA Committee on the Role of Medicine in Society. Calif Med 116:71-95, Apr 1972.

It is quite useful to think of these threads as being woven together to form the fabric of society. If they are strong and woven well, the fabric will be strong and so the society. If the threads are weak or poorly woven, the society will be weak, and perhaps confused and disordered. If one examines today's society in this way, it appears that the fabric and even some of the threads leave much to be desired. All of the threads which have been discussed represent human institutions which in today's society are under considerable stress, as are the relationships which weave them to one another.

Each of these major human institutions appears to have fallen short of the current expectations and needs of people. Traditional beliefs, values, morals and ethics are being eroded, and the churches themselves seem sometimes to have feet of clay. The military and the police are subject to unprecedented public criticism and disapproval, and are sometimes actually hard put to carry out their essential responsibilities. The courts are clogged, many laws appear impossible to administer, others are ignored and there has been an alarming tendency both in government itself and among dissidents to take the law into one's own hands. The educational system has been under attack because of public dissatisfaction with its performance. It seems likely to undergo substantial change, indeed is already experiencing increasing difficulty in getting adequate support whether public or private. And of course medicine has been particularly singled out, publicly castigated and actually discriminated against for its failure to measure up to unrealistic and impossible public expectations.

In all of this there is much to suggest that the fabric of today's society is substantially weakened although so far it has not actually come apart, except on occasion here or there. But it seems that the same cause can be ascribed in each instance. None of these professions nor the human institutions they dominate have yet been able to cope effectively with the problems of growing technologic and human interdependence, nor does any ready means of coping seem to be at hand.

It was suggested earlier that the thread of medicine might be one of the strongest. In any case there is much to suggest that medicine can and should begin to play a stronger and more important role. For many reasons, health and illness cannot really be separated from health care or from the disorders of human institutions and of human society. Perhaps the most basic reason is that these institutions and today's society are really nothing more or less than the works of human nature and human behavior, and it may well be that their disorders can be understood or corrected only in terms of human nature and human behavior. If this is true, as seems likely, then progress can only be made at the scientific level when psychology, sociology, economics, political science and jurisprudence are studied and explained in terms of human nature and human behavior, or human biology. The biological character of all that is involved in the problems of human society and their relationships to health, illness and the quality of human life assures that medicine will be deeply and intimately involved in these developments in science.

Until the sciences develop, and even after they do, the practical approach must still be "clinical." Both medicine and society must make do with what they know and what they have. The thread of medicine already touches many of the other principal threads in the general fabric. Even now, medicine is deeply concerned with cultural beliefs, value systems, changing ethics; with hostility, aggressive and violent behavior; with aberrant behavior, criminal justice and all kinds of legislation that affects or might affect health; with health education of the public and research and education in medical science; and with personal health, public health, the quality of life and the ability to do something about ill health. The thread of medicine is even now woven in and among the other essential threads of human society and already it can be seen to be enhancing the strength of the other threads.

But the problems are by no means solved. The new technological and human interdependencies now require a stronger and yet more effective presence of medicine throughout the fabric of society. There is no precedent for what needs to be done and no organizational model to copy.

How CMA is Beginning to Strengthen the Thread of Medicine and to Weave It Through the Fabric of Society

It has been suggested in this communication that the California Medical Association is evolving into a new kind of organizational instrument, one whose presence is to be found in more and more of the major areas where humans and their institutions must act and interact in today's complex and increasingly interdependent society; and it is developing a growing capacity to know what it believes should be done and a growing skill and technology to do it. The emphasis has been on improving the competence and effectiveness of the practicing physician, of the medical profession as a whole in its relations with the society it serves, and of the CMA itself as an organizational instrument in the California scene. Much has been accomplished and the purpose here is to attempt a brief analysis of what has been and is being done. For convenience, this is divided into what is being done to strengthen the thread of medicine and then what is being done to weave it through the fabric of society.

It is probable that only a few members of CMA fully realize what CMA is beginning to accomplish and its very considerable significance.

Strengthening the Thread

To strengthen the thread of medicine the CMA has pioneered the revival of the scientific authority of organized medicine, and in addition the development of a sound data base for medical practice and health care for the profession; it has begun to cultivate its base of support in society by identifying itself by word and deed with what it believes to be the patient's interest and by accurately informing public opinion; and, it is continuously seeking to improve the competence of the association as an organizational instrument in the framework of modern society, and of its members as physicians bringing the benefits of modern medicine to their patients.

The Science and the Data Base. If physicians or a medical association are to render opinions which will be authoritative and accepted as such in today's society, these opinions must be based on solid and up-to-date medical science and the most accurate health care data possible. The CMA's Scientific Board and its Scientific Advisory Panels and the Bureau of Research and Planning uniquely perform these two functions in organized medicine. The Scientific Board with its Advisory Panels for every specialty reflect the best scientific opinion from eight medical schools, a variety of scientific specialty societies and the Scientific Sections of the Scientific Assembly of the CMA. There is no comparable resource for scientific opinion upon questions of medical science and medical practice to be found anywhere in organized medicine. The Bureau of Research and Planning is CMA's principal means for developing and disseminating accurate information and data with respect to medical practice and medical care. It, too, is a "first," and it has now earned a national reputation. The Bureau of Research and Planning has placed its greatest emphasis on research, and its data base makes it possible in CMA to render informed opinions and to take authoritative stands on questions of medical services and health care. While these are the principal sources of scientific information and practice data within CMA, there are also many commissions, many committees, and many staff members with special competence and expertise. When all these are taken together, there is no longer any doubt about the authority of the scientific and practice data base upon which CMA renders opinions, participates in decision making, and takes action.

The Support Base in Society. CMA learned some years ago that medicine can no longer rely upon the prestige of the physician or of the profession to carry the day, whether in the care of a patient or in the solution of a social, economic, political or legislative problem. Elitism does not count for much and may even be counterproductive in this day of social egalitarianism. The direct economic force which physicians themselves can use to influence today's economy is pitifully small and generally ineffective, and at the ballot box physicians have one vote in a thousand, a fact that is not lost upon politicians. It therefore becomes necessary for physicians to substantially broaden their base of support if medicine is to be effective in today's society.

CMA was among the first of the major professional organizations to come to grips with this fact and to understand that, to "serve humanity" as a professional organization in this day and age, it would be necessary to gain the support of many other organizations where common interests were involved, and also to gain the support of public opinion. This understandably has been slow in accomplishment, but much has been achieved. There is now good reason to believe that public trust and confidence in CMA is becoming an increasingly effective force. The initial step was a conscious abandonment of the role of CMA as merely a physicians' protective association, and simultaneously a recognition of the basic truths that only physicians can really speak for patients and that what is best for the patient and his health care is always in the long run best for the physician and for medicine. Thus the way was cleared for CMA actions directed openly and wholeheartedly in the patient and public interest throughout the gamut of scientific, social, economic, political and governmental areas of activity. This enormously strengthened medicine's and CMA's identification with people, which next to its scientific and practice expertise is its most important source of strength. No doubt there is much more that can be done to broaden and deepen this identification, but a good start has been made and it is already bringing rewards in the form of more understanding and support in public opinion. Among the means which have been used to accomplish this are CMA-sponsored advocacies in the patient and public interest, teamwork with other agencies and organizations to achieve common goals, and most recently a beginning toward some acceptance of the principle of public accountability which is an essential companion to continuing public trust and confidence. When this has developed to the same extent as has advocacy and teamwork, public support will be far more secure, provided of course that motivation and performance are both always good.

Professional Competence. Continuing competence for both the association and its members receives an unusual amount of attention in CMA. This is of particular importance because the thread of medicine in the fabric of California society can be no stronger than the competence of the profession as a whole and of its professional association and its members.

CMA has pioneered programs of professional competence assurance through its now huge program of certification of the continuing education of practicing physicians and its comparably large program, with the California Hospital Association, of inspection and accreditation of medical staffs and hospitals throughout California. Both these programs have attracted national interest and have done much to demonstrate the willingness and capability of the profession to assure the public of its continuing educational and practice competence. In the field of practice competence, CMA has also pioneered peer review and is developing and refining this process in the conviction that only physicians are really in a position to judge the work of physicians. While none of these programs has yet provided any final solutions to the problems posed, all have a degree of sophistication and of effectiveness hardly to be matched elsewhere.

To assure its continuing competence as an organization, CMA has experimented with various modalities. For example, there have been three Planning and Goals Conferences for continuing education which resulted in the present pioneering programs. There have been a number of Council "retreats" or planning sessions which have emphasized planning and the evaluation of accomplishment. The CMA staff undergoes almost continuous self-assessment and organizational refinement to better achieve the goals of the association. And there is a continuing Committee on Organizational Review and Planning which is charged with constantly reviewing and shaping the CMA organization as its functions and responsibilities evolve, and to recommend indicated changes to the Council.

These then are a few of the principal activities which strengthen the association's capability to be effective in today's society and, taken together, they constitute an impressive new kind of organizational approach to creating the strongest possible base from which to render better service to humanity.

Weaving It Through the Fabric

To the extent there is the knowledge, the support and the competence available, it then becomes possible for an organization to develop the technology and resources for the actions which are necessary if a professional association is to perform effectively in today's complex and interdependent society. For a medical association this can be expressed as weaving the thread of medicine through the fabric of society. CMA has begun to do this in a fashion which recognizes many of the technological, social, economic, political and legal ramifications of medicine throughout society. The organization has undertaken the development of medicine's potential in each of these ramifications, and through the various branchings it has begun to use technologic, social, economic, political and legal means to achieve its goals. The goals for medicine are of course better patient care, betterment of the public health, and professional service to humanity. All of this is now being done by CMA on a scale which is quite unique for a professional association and with a scope which is beginning to get a real grip on the problem of coping more effectively with the baffling complexity and interdependencies of a still independent society. What has been and is being done is as follows.

The First Step—To Become Action-Oriented. This first step seems to have been taken over a period of several years when CMA gradually shifted from what was primarily a resolution-oriented association to one that is now primarily action-oriented. This occurred when it became evident to both the membership and the leadership that the traditional prestige and authority of medicine and the medical profession was no longer enough to carry the day on virtually any public issue concerning health and health care. With this fundamental reorientation there came a need not only to develop the profession's strengths as described above but also to develop new skills and new technology for effective accomplishment in the real world of modern society.

An Ideologic Basis for Action. The CMA has not yet formally established an official ideologic basis for its action and behavior, other than its tacit commitment to the principle that what is best for the patient is best for the physician and the medical profession, and to the basic aims of all practicing physicians, which are to try to relieve suffering, strengthen what is weak, repair what is defective and do no harm. These aims are quite as applicable to health care delivery and to the problems of health and the quality of life in society in general as they are in the care of any patient; and they have proved to be quite acceptable and sufficient to motivate the CMA and its membership for action.

Decisions for Action. An essential prerequisite for action is to decide what to do. The process of decision-making in CMA has been undergoing improvement and refinement as medical science, current practice data and other accurate information are brought more effectively to bear. Increasingly the House of Delegates, the Council and the officers have become more knowledgeable and are being presented with better information upon which to make decisions. The result is that the decisions reached are generally sounder, more apt to be innovative, realistic and clearly expressible in terms of the patient and public interest. After a sound decision has been reached and what is to be done has been determined, it then becomes possible to carry it out through the exercise of action tactics within the social, economic, political and governmental modalities of society. These action tactics have begun to develop some considerable sophistication in CMA, and the results have begun to show. Precisely what is being done is being described elsewhere in this special issue of CALIFORNIA MEDICINE. Some of the more important kinds of action tactics are discussed as they appear to be the means CMA is using, and using quite effectively, to increase the influence of medicine throughout the fabric of society.

Action through Social Influences or Pressure. Social influence or "pressure" is exerted primarily through communication, personal contact and persuasion. This can be effective if what is sought is reasonable, if the supporting arguments are valid, if it is consistent with the patient and public interest and if there is public sympathy with the organization and its purposes. CMA has major programs to strengthen its social influence in these terms not only through public information disseminated in the communications media but through direct contact and communication with many influential groups and organizations in both the public and private sector. These contacts and communications are not only essential for informing, persuading and convincing various individuals or groups, but also for creating a better informed public opinion and the all important support base in the non-medical community which medicine must develop and maintain if it is to be effective in society.

Action through Economic Influence or Pressure. Economic pressures are being exerted with increasing frequency and impact in the health care field by some professional providers such as nurses and house officers; by labor unions, which act both in the manner of labor unions to achieve improved benefits and wages for health care workers and in the fashion of management when they function as large-scale purchasers or "consumers" of services; and by government, which has imposed discriminatory restrictions and economic sanctions, both on services to patients and on fees to physicians. CMA has imposed upon itself the restriction that it will not condone a strike against patients or use economic tactics that will be harmful to patients; and therefore it seeks other means of exercising economic force or counterforce in the rough and turbulent world of economic pressures. To date, CMA has developed substantial expertise in the field of medical economics, and the thrust to date has been mainly to help develop workable solutions to as many of the economic problems of health care as possible. The CMA Relative Value Study of physicians' fees has become a model for the nation and is probably considerably responsible for the survival until now of flexible fee-for-service in private practice. Utilization review of medical services, coordinated by CMA but largely carried out by component medical societies and hospital medical staffs, has helped to control costs and has enabled the decisions with respect to patient care to remain in the hands of practicing physicians who in the last analysis are best able to make decisions concerning the appropriateness of services rendered to patients. However, CMA has yet to develop a truly realistic and effective technology for economic counterforce to match the pressures on physicians and patients, though it may soon be spurred to do so by forces now developing in both medicine and society.

Action through Political Influence or Pressure. In the terms of this discussion political action refers more to what is involved in accomplishing "the possible" in situations where there are conflicting interests, opinions and values, rather than action through pressure or influence on government which is considered separately. CMA realized long ago that the medical profession, representing only one in a thousand of the population and often divided within itself, is seldom if ever in a position to achieve its purposes through sheer power of numbers. Its political aims must be accomplished by the logic and reasonableness of what it proposes to do and by enlisting the help and support of others. This support must be won first by demonstrating a record of good performance in the public interest, and then by persuasion through a logical and effective presentation of whatever case is to be made.

There is substantial evidence that CMA is becoming an increasingly effective political force in California, in both the public and private sectors. It is finding ways to integrate the strengths of its special professional knowledge and expertise with its growing base of support and to develop skills for effective advocacy in the political arena. These skills basically include an increasing tendency to consult and coordinate with others whose interests may be involved in the decisions to be made, only undertaking what can be seen to be in the patient or public interest, and only that which is politically possible to achieve. When a decision is reached for a political action, then whatever is to be done is vigorously pursued by bringing the authoritative knowledge and professional expertise of the association and its members to bear, drawing upon the strengths of its support base for whatever help may be needed, and using communications, personal contacts and persuasion to influence whomever should be influenced, and where necessary, negotiating from as much strength as possible. Political action or advocacy such as this is best done by skilled persons who must assure themselves that the aims sought are reasonable, the supporting arguments valid, and the whole consistent with the interests of the profession, the beneficiaries of the advocacy whoever they may be, and the public.

It is by these means that CMA acts to "accomplish the possible" through political influence or pressure in both the private and public sectors. The results are by no means perfect but there is good reason to believe that the political strength of CMA has greatly increased and that its influence throughout the fabric or framework of society probably already exceeds that of any other professional association. There is no doubt that CMA has become a force to be reckoned with in the politics of health care in California.

Action through Influence or Pressure on Government. The support base for CMA influence and pressure on government is not founded upon the voting power of the membership nor upon the self-interest of physicians. Rather, the support base for these activities lies in the growing respect shown for CMA performance in the public interest, the growing support of public opinion in California for much of what CMA is trying to do, the coordination of effort with other organizations where there are similar or identical aims, and the campaign support which CALPAC and AMPAC have given candidates seeking elective office and who have the support of the physicians in the constituency from which they were elected. Campaign support of a candidate by CALPAC or AMPAC should not and does not mean that medicine will control his actions but it does almost always assure that he will listen to medicine's views, and this is important. The support base is further strengthened by direct contacts and visits by CMA members to both state and federal legislators and executives. CMA influence or pressure on government may be directed toward the administrative, legislative or judicial branches at state or federal levels. The technology and skills which have been described for social, economic and political action are employed. For some time these activities were primarily at the state level but recently CMA has developed a presence and an influence which is beginning to be felt at the federal level in Washington as well.

At the state level CMA has been in dialogue and negotiation with the executive branch for many years on many matters of the public health and the delivery of medical services, and most recently has participated with some good result in discussions about the reorganization of the Department of Health Care Services. This is not the place to chronicle or to catalogue the ups and downs and the successes or failures of these dialogues and negotiations. The point to be made is that CMA is listened to and does have input into what is done—although somewhat less than the association would like or believes it should have. At the federal level, similar dialogue and negotiation is being developed with the Department of Health, Education, and Welfare, and particularly with the Social Security Administration with respect to the provisions of PL 92-603 (formerly called HR 1) which has profound implications for physicians, medical practice and patient care.

Legislative action is a highly developed function of CMA at state level and is a rapidly increasing influence on legislation which is before the Congress. The hundreds of bills introduced into the California Legislature each session which pertain to health are screened by CMA staff and reviewed by the Commission on Legislation, following which the Council decides whether to support, watch or oppose each bill. The growing political wisdom, skill, and political strength of CMA is reflected in the truly remarkable success which has been achieved in working with the Legislature to develop good and useful legislation in the field of health care. CMA-sponsored bills in the Legislature have also had an impressive record of acceptance and success. At the federal level the Committee on Federal Legislation monitors important federal health legislation which might affect medicine in California. In each instance the techniques and technology which are used to influence legislation are those which have been developed for political action, and the results have improved as these have been refined.

In one instance CMA has resorted to a court action to have certain administrative actions by the executive branch of the state government declared illegal. This suit was brought in behalf of the beneficiaries of the Medi-Cal program who, CMA believed, were deprived of adequate care by the administration actions which had been taken. There was broadly based support for this CMA undertaking, and the suit was successful and the services restored. As a by-product of this successful court action carried on in the patient and public interest, the political stature of CMA was enormously enhanced.

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Yes, the threads of medicine are indeed being strengthened and they do indeed weave through the fabric of society with all of its technological, social, economic, political and legal or governmental ramifications. Further, this is by no means a passive thread but one that is vibrant, active and with great capability not only to strengthen the societal fabric but to improve health, well-being and quality of life for the members of society. And finally, it is evident that CMA is developing the determination, the knowledge and the skills to strengthen the threads of medicine and to weave them more and more intimately throughout the fabric of today's society. In so doing, it is itself developing into a new kind of professional organization.

Some Possibilities for the Future

CMA has made remarkable progress as a new kind of organizational instrument with which an essential profession—in this case medicine—can exercise influence throughout the fabric of modern complex society with all of its growing interdependencies which inevitably increase in spite of the strong tradition of independence among its various elements. What is being done should obviously be continued; but on the basis of what has already been accomplished it is suggested that it may soon be time for CMA to give some attention to still other matters which, if attended to, would surely strengthen further the scope and effectiveness of CMA activity within the framework of today's society:

Public Accountability of Stewardship

The principle of public accountability of stewardship has not yet been fully accepted by CMA but it goes part and parcel with leadership in health care and its accompanying responsibility both to patients and the public. It seems likely that the time will soon come when it will be necessary for medicine to accept the principle of public accountability and to carry it out faithfully and well if the profession is to continue to enjoy the trust of the public. Frank and open public accountability can also be a useful means of sharing both successes and problems in health care with patients and the public.

More Involvement in Decision Making

The Sixth Progress Report of the CMA Committee on the Role of Medicine in Society identified participation in decision making at all levels of health care as an important function of practicing physicians. This is not to say that physicians alone should make these decisions. In fact they seldom do. Even in patient care they must secure the informed consent of the patient except in the most critical emergencies. But many of the impractical, unworkable and costly things that government and others have been foisting on medical care might have been considerably less impractical and unworkable if practicing physicians had had more of a say in the decision-making process. It is suggested that CMA might begin to press even more vigorously for more involvement of more knowledgeable physicians in decision making at all levels of health care both in and out of government.

Representing the "Consumer" in Health Care

It has frequently been pointed out that most of those who purport to represent the "consumer" in health care really do not and cannot. The true consumers of medical services are patients, and practicing physicians are in a better position to understand the needs of the whole spectrum of patients than are legislators, labor union leaders or self-styled or otherwise appointed consumer representatives whose direct contact with patients and their needs is usually quite limited and often very personal. It is suggested that the time may be at hand for CMA to begin working specifically toward a stronger identification of the physician and the medical profession as spokesman for the true consumers of medical services, who are their patients.

The Physician and Human Individuality

There are few organizational spokesmen for human individuality in today's society. Most organizations tout one or another kind of group or collective interest. Yet these are times of apparently growing emphasis on human dignity, personal fulfillment and doing one's own "thing." This is a new societal emphasis on human individuality. The validity of these attitudes is supported by the fact of the biological uniqueness of every individual, and it is this very uniqueness with which the physician deals in patient care. It is the adjustment of this uniqueness to the problems of life and living or the lack of it that determines a person's state of health and well-being. It is suggested that CMA and medicine might move toward a stronger professional identification with the concept and the reality of human individuality and uniqueness, and that there might be strong support if the profession were to espouse the cause of individuality in today's increasingly interdependent society. There is no other organized profession or group which seems so well suited to champion human individuality in the technological, social, economic and political arena of our time.

Value Systems and Ethics

Much more than it has in the past, decision making for the physician in health care in the future is certain to involve value systems and ethics as well as medical science and expertise. Scientific values, humanitarian values and economic values often come into conflict in health care, and this increases and even becomes critical as costs rise and when resources become scarce. Changing societal values and progress in medical science have already profoundly affected ethics and they will continue to do so. CMA has begun to address some of these problems through its pioneering Committee on Continuing Study of Evolving Trends in Society Affecting Life. However, there are other values which apply in greater or less degree when decisions are made in health care, and it is suggested that CMA study scientific, societal, humanitarian, and biological values in medical and health care with a view to finding a means of assessing the extent to which each of these value systems should be applied when decisions of various kinds are made at various levels in medical and health care.

Cost Benefits

The issue of what benefits are to be derived from what costs in medical services and health care is certain to become increasingly important in many decision-making processes in which physicians and the medical profession will participate. Whether caring for a patient or rendering opinions on the health related problems, physicians and the medical profession will need knowledge and expertise to define and defend the benefits to be derived from expenditures for medical and health care services. It is suggested that CMA should tackle this complex subject about which little is yet known as a service both to its members who must decide or give an opinion as to the right thing to do, and to patients and to society who must foot the bills.

On Looking Ahead

CMA shares a serious weakness with many other democratically governed organizations and institutions in today's society, including government. This weakness lies in the difficulty of identifying and doing today what should get done today if one is to be in a position to deal effectively with tomorrow's problems when tomorrow comes. Much that should be done to prepare for tomorrow's problems requires a good deal of lead time, often of a decade or more. Democratic societies, whether medical associations or governments, are by nature much more oriented toward the present than the future and tend to think and act only from annual meeting to annual meeting or from election to election. There are no built in warning devices to call attention to the problems of the future and no very good mechanisms to assure sustained action in the continuum of time. Somehow there should be developed an instrumentality which will be responsive to the democratic system and yet make it possible for it to look ahead, to assess the problems to come, and to get done what needs to be done now to prepare continuously for what can be seen to lie ahead. Societal interdependence is not only for today. It extends into the future as well and can only become intensified. It is quite conceivable that the ultimate survival of democracy, whether in medicine or in society, will depend on how well it can bring the future as well as the now into its deliberations and its actions.

CMA has taken some steps in this direction but it has yet to develop an effective mechanism or "guidance system" capable of taking sensings and feedback from both the present and the future and building them effectively into the decision-making processes of the association. If undertaken, this too could be a pioneering effort for CMA.

It is suggested that the above are some possibilities of things CMA might begin to do at this time to strengthen further the threads of medicine in the fabric of society and the influence of CMA as a professional association working for the betterment of health and health care in California.

Looking Further Ahead

Looking further ahead, it seems likely that there will be yet a further breakdown and erosion of many of the traditional threads or sinews which have held this human society together. The churches, the law, the military, and the educational systems as they exist no longer seem to be adequate to deal with the knowledge and technologic explosions and the new complexities and new interdependencies these have created. They are failing of success as human institutions to solve human problems and they are being ignored or bypassed by the public and even the government to an unprecedented extent. Medicine, however, seems to be a curious exception. It has succeeded rather than failed; indeed its problems are those of success. And the public, far from ignoring or bypassing medicine, seems to be looking to it for the solutions for all its problems. Unfortunately, these are beyond the capability of medicine to solve alone although it may have something to contribute to the solutions.

It remains to be seen whether we are now witnessing the beginning of another fundamental revolution in our civilization comparable to the scientific and industrial revolutions which have produced the enormous explosions of knowledge and technology with which we are coping or not coping today. If we are at the beginning of such a revolution, and there is much to suggest that we are, then perhaps it will be the one which develops new values and new methods of coping with the technology and societal interdependence which the scientific and industrial revolutions have produced. Perhaps one can even now begin to speculate upon what this new revolution might be about and upon what the new values might be like.

It seems possible to identify some of the essential elements with which new values in a new kind of society must be prepared to deal. Three seem obvious enough. First there is the mass of new knowledge which is the continuing product of the scientific revolution. Second there is the mass of new technology and the growing dependence on it which is the continuing product of the industrial revolution. And third there is the recognition of the reality of the closed earth biosphere and all this implies for now and for the future of humanity. It takes little profound insight to realize that human nature and human behavior are the keys to success or failure for whatever kind of society is to arise from the failure of existing institutions to cope with our problems, and that whether it will be success or failure will depend on how well it handles knowledge, technology, the closed biosphere and human behavior. It is important and probably even essential to note that in the final analysis these are problems in biology—human biology, that is—human nature, human behavior and human adjustment to the human and physical environment. And if there is to be health and well-being within the context of such a biological society, then the knowledge and professional expertise of medicine cannot but be involved.

In support of this thesis, it may be noted that much of where the action is today seems to be in the field of biology. The new emphasis on sexual fulfillment, on population control toward a zero growth, on control of land, air and water pollution and resource conservation, all seem to recognize the biological nature of man in his relationship with his environment. Further evidence for the emergence of new values is the new emphasis on self-interest and personal fulfillment for oneself and for others, the philosophy of "I'm OK—You're OK," and increasing attention to the quality as well as the duration of life. What is emerging from all of this may well be in fact a biological society, and what we are presently undergoing may well be a biological revolution of comparable scope to the scientific and industrial revolutions which in this view will give rise to this new biological society. It seems possible that this may indeed have come to pass by the end of this century; and, if so, then knowledge, technology, social, economic, political and governmental activities will all come to be considered and dealt with in terms of human nature and human behavior in the closed earth biosphere—in other words, in terms of human biology.

Medicine would play a very central role in such a biological society because of its authoritative knowledge of human nature and human behavior and its expertise in the field of health and disease. Health for a biological society and its members will be fully as important as personal fulfillment for each member. In a biological society, physicians and the medical profession will surely be rendering opinions, participating in decision making at all levels of such a society and performing a variety of old and new specialized professional functions. They will need to develop their knowledge base, their support base and their professional skills to be effective in influencing technological, social, economic and governmental action to restore and maintain health and to render their professional service to humanity.

CMA has already begun to lay the groundwork for this role.

Conclusion

The California Medical Association is becoming a new kind of professional association which is actually beginning to cope successfully with the growing human and technologic interdependence which came about as a result of the scientific and industrial revolutions and characterizes today's society. CMA appears to be pioneering new roles for an essential profession and a new kind of an organizational instrument to bring its influence to bear more directly and more effectively in many of the ramifications of society. This can be of enormous significance, not only as a societal phenomenon, but as a means of enabling a profession to strengthen its knowledge and expertise and bring these to bear and so render service to its members, their patients, to the public, and indeed to humanity.

Refer to: Thomas RL: CMA in action. Calif Med 119:18-37, Dec 1973

CMA in Action

ROBERT L. THOMAS
Executive Director

THE FOLLOWING PAGES outline the action programs of the California Medical Association—in other words, what it *does*. Before commenting on these reports on current CMA activities and accomplishments, I believe it is pertinent to explore the question of what the California Medical Association *is*. Put in the most basic terms, CMA is an organization of California physicians. Inherent in this simple definition of an extremely complex association are a number of its unique organizational attributes:

- CMA's purpose is to safeguard and improve the health of Californians.
- CMA's structure is representative of physicians throughout the state—clinicians of all specialties, educators, researchers, administrators, solo and group practitioners.
- CMA's policies are determined by California's physicians.
- CMA's influence often extends to the entire country because of the dynamic California environment to which it creatively responds.

Each of these concepts bears closer examination.

Purpose

When a handful of family doctors founded a state medical association for California in 1856, they established a Constitutional purpose that continues to provide a solid basis for the activities carried on by today's CMA: "To promote the science and art of medicine, the protection of the public health, and the betterment of the medical profession." In that purpose, the present-day California physician recognizes his growing responsibility to lead the way in solving health problems facing the public, and through his local medical society and the California Medical Association, he is meeting this obligation; and CMA also is meeting the needs of the individual physician by helping to shape and maintain an environment in which he can render the highest possible quality of medical care to his patients.

Structure and Policy-making

The 25,000-member California Medical Association is composed of the members of 40 component county medical societies.

CMA policies are established democratically either by action of its House of Delegates or the Council. Membership of both the House and the Council is determined by elections at the local level throughout the State.

The House of Delegates, CMA's major policy-making body, meets annually to consider resolutions and reports of the Council, Commissions and Committees. The House consists of more than 300 member physicians who have been elected by the members of component societies. Each society has proportionate representation with a minimum of two delegates. Last year alone, the CMA House of Delegates established policy in some 200 vital fields.

The 31-member Council acts on policy matters in the period between meetings of the House of Delegates. The Council consists of officers who are elected by the House and of councilors elected by their districts, with this election confirmed at the House of Delegates annual meeting. Again,

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representation is proportionate, with each Councilor District being entitled to at least one councilor. The Chairman of the Scientific Board and the Editor of CALIFORNIA MEDICINE are also key members of the Council. The Council meets approximately every eight weeks and often takes action on more than fifty separate issues during each of these deliberative sessions which usually last seven or eight hours.

Any CMA member may bring his thoughts to bear on formulation of CMA policy decisions. Policy recommendations for the House of Delegates are presented in the form of resolutions, which may be introduced by a county society delegation or by individual delegates (on their own behalf or on behalf of their colleagues). There are numerous channels through which recommendations for policy decisions can be brought to the attention of the Council. The most common is for CMA's hard-working Commissions or Committees to determine that an action should be taken in their respective subject areas (legislation, communications, community health, scientific and educational matters and the like) and to submit a formal written report to the Council containing specific recommendations. Recommendations for action also may be brought to the attention of the Council by a member or a county medical society through individual correspondence to his district Councilor, the chairman of the Council, the president or the chairman of a Commission or Committee. In addition, allied health organizations may request the Council to consider subjects for action. Both in formulating and in implementing policy, CMA maintains active liaison with more than 75 other health-related organizations, plus the myriad state and federal governmental bodies concerned with health.

CMA's 85 Commissions and Committees deserve special recognition. Appointed from lists of candidates submitted by local societies, they not only study and make recommendations on countless vital issues, but also implement policy directives of the House and Council with the assistance of the CMA staff. Some 1,000 physicians—one out of every 25 CMA members—is involved in Commission or Committee work. Nearly every day of the year at least one CMA committee is meeting somewhere in the state. An estimated 15,000 physician-hours are voluntarily committed to these working sessions annually. The work of CMA committees has written much of medicine's history in the state. These committees, and comparable county medical society committees, offer individual physicians the best opportunity to serve the profession and the public beyond their patient care responsibilities.

Influence

The review of activities and accomplishments which appears in the following pages reveals that CMA programs often become prototypes for the nation. In many ways, California acts as a representative cross section of the nation as a whole. Perhaps more than any other state's, California's population represents virtually every section of the country, every social and political view, and every economic level and ethnic background. And that population, which already accounts for one-tenth of the U.S. total, is growing at an astounding rate. It is estimated that California's population will reach 40 million by the year 2000—more than doubling by the end of the century. It is not surprising, then, that health care challenges, like other challenges, often come into focus first in California. CMA's pattern of constructive leadership in anticipating and developing solutions to these challenges has placed it in the forefront.

There is one factor which perhaps more than any other accounts for the continuing strength and influence of the California Medical Association. In spite of increasing social, economic and political challenges, CMA has never lost sight of its basic identity as a *scientific* organization. Its fundamental concern and unique area of expertise is the science and art of medicine—making sick people well and keeping them healthy. When CMA brings its influence to bear on public opinion and public policy-making, its scientific commitment and knowledge is the foundation upon which its credibility rests.

In an era of increasing computerization and depersonalization, CMA as an organization has not forgotten what its individual members will always know: that any "system" of medical care must be judged by the effect it has on the *art* of medicine, that medical care is given to a patient—to one human being at a time by another human being whose training and concern make him a healer.

In view of the foregoing, it seems appropriate that Chapter I of "CMA in Action" should outline the Association's scientific and educational accomplishments. In this chapter, the unprecedented work of CMA's Scientific Board is highlighted, with special emphasis on its programs which certify physicians' accomplishments in postgraduate education.

Chapter II deals with the highly inter-related activities of CMA in "Safeguarding Quality of Care." The association's many-faceted peer review program is far from new, but with the advent of PSRO's (Professional Standards Review Organizations) mandated by federal statute, CMA's growing record of accomplishments in professional self-evaluation and control is particularly relevant.

Chapter III, "Government Advocacy," describes CMA's effectiveness in bringing Medicine's views to bear on health care legislation at both the state and national level. It also covers the association's expanding advisory role in relation to administrative agencies at both levels. In addition, this chapter deals with the vital activities of the California Medical Political Action Committee (CALPAC), through which physicians and others actively support state and federal political candidates who are constructively concerned about the delivery of quality medical care.

"Improving the Availability of Care" is the subject of Chapter IV, which covers CMA's views and efforts in several important areas of concern to the public and the profession: cost of care, health manpower distribution, and national health insurance.

Chapter V brings into focus the wide variety of CMA activities which attempt to deal with health at its most basic level—the attitudes, knowledge, life-style and living conditions which ultimately have a far greater influence on the total health of an individual than the medical care he receives once he is sick. In this chapter, entitled "Shaping a Healthier Environment," CMA's growing concern with social needs (which often result in medical needs) is explored.

Chapter VI, "Serving the Membership," concentrates on the CMA services which directly benefit the individual member, as contrasted with the association's programs as a whole, which serve both the profession and the public. Included in this chapter are CMA's efforts to relieve the professional liability problems which face physicians.

The final chapter, entitled "Planning and Evaluation," covers the means by which the association anticipates problems, sets its goals, channels its resources into well-defined fields of long-term commitment and constantly re-examines its organizational effectiveness.

CHAPTER I

Advancing the Science and Art

Since its inception more than one hundred years ago, the California Medical Association has been committed to the furtherance of scientific medicine and the promotion of increasingly effective patient care. In the last two decades, however, a number of factors—including the swelling involvement of government and other third parties in the health care arena—stimulated CMA to direct its attention more and more toward the socioeconomic aspects of health care. This activity has been necessary and productive, as subsequent chapters of this article will relate. But early in the 1960's CMA's leadership recognized that the association's growing strength in socio-economics must not be allowed to threaten its stature as a scientific organization and that, in fact, CMA's pre-eminence as an authority in the "art and science of medicine" is the real basis for its ability to speak authoritatively to the public on vital issues concerning the ways in which health care should be organized and financed.

Consequently in 1961, the Council established a "blue ribbon" committee to study this problem and recommend appropriate action. Led by Doctor Dwight L. Wilbur, former editor of CALIFORNIA MEDICINE, the committee formulated a comprehensive set of recommendations designed to strengthen and formalize all scientific and educational activities carried on by CMA, so that these activities would not be gradually eclipsed by socio-ecnomic concerns, and CMA would maintain the scientific eminence necessary if it is to speak effectively for medicine in California.

The Scientific Board

In 1963 the Wilbur Committee's report gave birth to a unique organizational entity among state medical associations: CMA's Scientific Board. During the past ten years, the Board has made increasingly dramatic strides in developing, coordinating and strengthening the scientific and educational activities of CMA, drawing together all medical scientific organizations in California in mutual cooperation.

The Board's carefully designed structure has been instrumental in its success. Membership in CMA automatically qualifies a physician as a member of one of the association's Scientific Sections, which include: Allergy, Anesthesiology, Chest Diseases, Dermatology, General and Family Practice, General Surgery, Industrial Medicine, Internal Medicine, Neurology, Obstetrics and Gynecology, Ophthalmology, Orthopedics, Otolaryngology, Pathology, Pediatrics, Physical Medicine and Rehabilitation, Plastic Surgery, Preventive Medicine and Public Health, Psychiatry, Radiology, and Urology. The Scientific Board is composed of 42 members selected from nominations by these 21 scientific sections and 16 recognized specialty societies. Thus, the Board draws together elements that otherwise might tend to be divergent or even at cross purposes.

As the contributions of the Scientific Board have become increasingly visible, CMA leaders have given it an increasingly influential role to play in the overall policy-making functions of the association.

The Chairman of the Scientific Board now sits as a voting member of both the Council and the House of Delegates. In addition, 21 members of the Board serve ex-officio as non-voting delegates to the House, and the remaining 21 members are alternates. Caucuses of the Scientific Board are held during the Annual Scientific Assembly (which meets in conjunction with the House of Delegates), so that resolutions coming before the House may be considered and recommendations made.

Throughout the year, 13 committees and 21 Advisory Panels—one for each Scientific Section—work under the direction of the Scientific Board.

The Advisory Panels

The first Advisory Panels were organized in 1968 to serve as a scientific and educational resource to CMA Scientific Sections. Since that time, all 21 panels have been activated and have expanded the scope of their activities so that they constitute an invaluable resource not only to CMA as a whole but also to other major health organizations in the state.

Each panel is composed of selected members of its Scientific Section of CMA, appropriate Scientific Board members, the principal officers of the scientific specialty society at the state level, and the chairman of the appropriate department of each of California's eight medical schools. More than 330 physicians are now involved in Advisory Panel work. By melding the expertise of the outstanding academicians and clinicians in a given specialty, the panels have brought into being a unique forum and have begun to reduce the fragmentation of the profession to a remarkable degree. Such involvement has drawn numerous prominent academic physicians to rejoin CMA after many years of lapsed membership. Interest in CMA's Advisory Panel structure has been widespread. Two years ago the AMA announced that it planned to have "Advisory Councils" to specialty sections by this year—patterned after the California model.

Among the many accomplishments of CMA's Advisory Panels are the following:

- Members of the Advisory Panels have developed a series of "Epitomes in Progress" which have been published monthly in CALIFORNIA MEDICINE. The series presents accepted recent advances in each field of medicine from this authoritative source in capsulated form. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of items of progress in a particular specialty which have recently achieved a substantial degree of acceptance—whether in his own field of special interest or another. Requests for reprints in unprecedented numbers attest both the value of the series and the expanding interest and readership of CALIFORNIA MEDICINE.
- Advisory Panels have recently begun responding to a new challenge: answering increasingly numerous requests for scientific opinions on medical practice questions posed to CMA by third party payers, local medical care foundations and others. By virtue of their composition, which brings together the foremost practitioners and scholars in a given specialty, the panels provide truly authoritative and representative opinion to bear on difficult questions such as classifying new procedures as experimental or acceptable medical practice.
- Advisory Panels provide the background materials for "Health Tips"—informational articles directed to the public and distributed in schools and elsewhere under the sponsorship of the California Medical Education and Research Foundation, a subsidiary of CMA. The Panels also review these public information articles in advance of their printing and distribution. No other organization in California—government or private—has at its disposal this caliber of broad scientific expertise underlying its health education efforts.
- Other important responsibilities undertaken by the Advisory Panels include: Advising the

Committee on Continuing Medical Education on specialized education sources and standards of credit for recognition of educational activities of specialty societies in the CMA Certification of Continuing Medical Education Program; considering scientific and educational elements of pending and projected legislation of mutual interest to CMA, specialty societies and medical schools, thus aiding the profession in achieving unity of position on a variety of subjects; assisting the Scientific Section officers in planning scientific programs of merit each year for CMA's Annual Scientific Assembly; and tackling special projects, such as the tremendous task of developing guidelines to help California physicians conform to the recent court decision on "informed consent."

Continuing Medical Education

Since 1934, CMA has sponsored its own postgraduate education programs to keep physicians up to date. These and other programs now are responsible for nearly 50,000 hours of instruction yearly. For many years, CMA has served as a statewide center for coordinating and publicizing postgraduate medical education sponsored by all participating organizations—hospitals, medical schools, specialty societies and others. In 1970 CMA officially launched a program to certify physicians' accomplishments in postgraduate education and to accredit these and other learning activities. In the three years since its genesis, the CMA Certification Program has attracted more than 10,000 *voluntary* physician participants, 18,000 forms have been received and over 2,000 certificates have been awarded to physicians successfully completing three years. CMA has set an interim goal of 18,000 physician participants by 1974, and is steadily working toward certification of all California licentiates.

The program is designed to encompass all educational activities, whether formal or informal, whether self-implemented or implemented by organizations, which ultimately lead to a continued or increased state of medical knowledge by the physician and, thus, to a high quality of patient care.

Successful efforts are being made to coordinate the program with similar endeavors of other scientific organizations in order to reduce the number of forms a physician must fill out. In this, CMA has achieved 100 percent reciprocity with the AMA. And the California Society of Anesthesiologists has adopted our program, requiring participation by all its members. Considerable progress also is being made in coordination with other specialty societies. Many hospitals in California are now requiring participation in CMA's Certification Program for renewal of staff privileges. More than 350 community hospitals and other organizations have applied for CMA accreditation of their continuing medical education programs and activities.

Audio-Digest

It has been 20 years since the CMA House of Delegates saw sufficient promise in a fledgling postgraduate enterprise called Audio-Digest Foundation to adopt it as a nonprofit subsidiary. Since then, it has grown from a local, small-scale experiment with weekly taped reports from medical journals and meetings for general physicians to twice-a-month subscription services for nine specialties. The number of subscriptions is now nearly 50,000. More than one and a half million dollars has been contributed by Audio-Digest to medical education since its inception in 1953. As an editorial writer in CALIFORNIA MEDICINE observed some years ago, "Lo: a benign cycle. Medical education is broadened as the number of subscribers increases, and the more subscribers the more revenues, and the more revenues the greater the cash contributions in support of medical education."

Conclusion

These accomplishments demonstrate the commitment of California's physicians to constant heightening of the quality of patient care through their own continuing study and self-improvement. CMA's Certification Program lodges within the medical profession, rather than in other hands, the task of assessing the adequacy of the continuing medical education of the physicians of California.

CHAPTER II

Safeguarding the Quality of Care

In California, the concept of "peer review"—the ongoing monitoring by a physician's colleagues of the medical care he provides—has been formalized and refined to the extent that it surpasses and has set a pattern for that of other states throughout the nation and other countries throughout the world.

To Californians, CMA's acknowledged leadership in this important field has meant and continues to mean assurance of the highest quality of care should they become ill. To physicians, these CMA activities provide a means for the profession to demonstrate to society through well-documented performance that medicine can effectively plan, implement and monitor its own activities without external controls.

Medical Staff Surveys

Perhaps the best known and most widely respected of CMA quality assurance activities is the Medical Staff Survey Program, begun in 1961. That year CMA became the first medical association in the nation to formalize a plan for hospital medical staff self-government and self-evaluation. Through the program, practicing physicians from CMA's medical staff survey teams join local community physicians to evaluate the care rendered and reviewed by hospital medical staffs. During each of the surveys, these teams of specially trained physicians analyze the organization of the hospital's medical staff, the adequacy of its records, its medical review competence, efficacy of its credentials review, procedures for determining medical and surgical privileges and other factors directly related to patient care and physician performance.

Failure of a California hospital to achieve certification has significant consequences. Eligibility for participation in the Medi-Cal program is contingent upon a hospital's obtaining either approval from CMA or accreditation from the Joint Commission on Accreditation of Hospitals (JCAH). The California Hospital Association made the CMA survey a provision of membership in 1969.

Since the inception of the program 13 years ago, CMA has conducted more than 800 hospital surveys and by the end of this year expects to exceed the 1,000 mark. The astounding growth of the program is best reflected in the frequency of surveys. During 1961-72, CMA averaged 64 surveys a year; currently the average is two surveys a day.

During 1973, CMA's survey teams joined lay surveyors of the Joint Commission on Accreditation of Hospitals to conduct "consolidated surveys" of the medical staff activities and the hospital facility concurrently. CMA is responsible for quality evaluation, and JCAH for environmental considerations. Initial results of this combined effort indicate that it is leading to increased efficiency and more thorough survey results to maintain high standards, thus preserving this function of quality review for the medical profession.

Surveys of Other Institutions

CMA recently embarked on a pilot program to inspect the quality of care in nursing homes. In preparation for this expansion of the survey concept, the association developed "Long-Term Care Review—A Statement of Principles," which is a corollary document to CMA's "Guiding Principles for Physician-Hospital Relationships," now a national standard in its field. Negotiations are currently under way with the state for California Medical Association contracts to survey all 1,400 long-term care facilities in California as well as psychiatric hospitals and health services in prisons throughout the state. Survey techniques will draw heavily upon the experience gained in the CMA Hospital Staff Survey Program. Emphasis will be upon the character and quality of care provided in the facilities. CMA's willingness to negotiate for surveys of these numerous and varied facilities, a massive and undramatic task, constitutes a strong reaffirmation of the association's commitment to quality assurance.

CHAMPUS Facilities

With the concurrence of the Department of Defense, CMA has begun a survey program for facilities providing specialized care to recipients of the Civilian Health and Medical Program—Uniformed Services (CHAMPUS). The types of services provided by these special facilities are care to the mentally retarded, physical rehabilitation, special education and psychiatric care.

Hospital Utilization Committees

When a CMA survey team goes into a facility, one of its main tasks is to evaluate the work of the utilization committee. These committees are recognized generally as the key to effective in-patient utilization review. Recently they have tended to emphasize ongoing as distinguished from retrospective review. Hospital committees spend thousands of hours annually in review of care and in liaison with other committees within the hospital. Review techniques vary considerably from one facility to the next, but all such committees are oriented to the patient's welfare.

Medical Audit Workshops

An important innovation of the CMA is the "Medical Audit Approach" in which intensive three-day workshops are conducted for qualifying teams from approved hospitals. The workshops search out specific areas of care in which there is room for improvement in quality and utilization—on a programmed basis. Remedies are then sought which can be applied to the whole spectrum of resources and services. The "problem-oriented" approach is achieving such promising results that CMA has scheduled monthly sessions during 1973 in response to growing requests.

County Medical Societies and Their Foundations for Medical Care

The cornerstone of all peer review activity is the dedicated committee participation of physicians *at the local level*—the level nearest the actual delivery of care. California physicians have led the nation in local peer review committee activity; some county medical society review committees have maintained continuity for more than 20 years. The Foundation movement itself stemmed largely from the desires of local physicians to assume greater local responsibility for the quality of care and utilization control in their peer group area. A recent survey of peer review activity throughout the state revealed that last year in California local physicians spent some 60,000 hours in peer review activities.

Tumor Boards

CMA has been active in improving care given to cancer patients since 1932. It does this by stimulating formation and operation of Tumor Boards (this group of specialists always includes a surgeon, an internist, a radiologist and a pathologist) in general hospitals. These boards maintain clinical and statistical data, including yearly follow-up reports on all cancer patients, which is essential to quality review. CMA sets standards for Tumor Boards, provides consultative services for new boards and survey boards when asked to do so.

Peer Review Commission

To further CMA's commitment to quality medical care, the Council took steps in 1971 to form a CMA Peer Review Commission as an extension of CMA's present activities—irrespective of impending federal legislation in this field. Basic factors underlying this move were the need for a single organization in California to respond knowledgeably regarding peer review efforts throughout the state as a whole and the need for CMA to stimulate and assist those component societies where peer review could be made more effective.

Since its formation the Peer Review Commission has responded creatively to its self-imposed challenge: ". . . to provide all possible support and assistance to local peer review activity; to maintain a functional appeals system; to coordinate diverse peer review activity; and to provide a communications network to facilitate peer review throughout the state."

Appeals Committee

The CMA Appeals Committee plays a vital role in reviewing decisions on quality, utilization and fee problems made by local county society review committees. These reviews are conducted at the request of any party to the local hearing—physician, patient, carrier, county society and others. Although CMA has long made this service available, the committee's activities were considerably refined and expanded when it became a key element in the newly created Peer Review Commission.

PSRO: Professional Standards Review Organizations

Recently CMA was confronted with a new federal law (PL 92-603), which mandated the creation of "Professional Standards Review Organizations" throughout the country by 1976. The association had waged a long battle against this federal PSRO concept, forcefully pointing out that existing peer review mechanisms in California were capable of doing the job. Once the concept became law, however, CMA assumed its share of responsibility to influence the development of regulations, pledging to continue to be a strong advocate in defense of the medical profession whenever regulations or administrative policies interfere with the practice of medicine. At the same time, CMA reaffirmed its commitment to strengthening and expanding already existing peer review programs throughout the state, so that the association would continue to be in a strong position to maintain a vital role for CMA and its component societies in quality care assurance.

Recently CMA has given particular attention to the services it should be prepared to offer to *component society sponsored* PSRO*'s*. CMA is continuing to develop its resources so that it can offer a comprehensive range of support activities: A statewide appeals system; scientific coordination and information exchange; professional resources clearinghouse—training and evaluation teams; CMA staff survey services; interdisciplinary liaison with allied health care providers; continuing education certification and accreditation; data center; and consultation—both initial and continuing organizational assistance.

Because the PSRO section of the law called for delineation of the geographical areas by January 1974, CMA quickly assumed leadership in developing a realistic "Master Boundary Plan" in cooperation with component societies, allied health provider groups and others. This coordination effort appears to have been productive. The CMA-developed plan was the basis for a hearing by the Department of Health, Education and Welfare on PSRO geographical domains for California; and recently the Region IX HEW Office announced that it had officially recommended CMA's Master Boundary Plan to Washington with minor modifications.

Medi-Cal Prepaid Health Plans

In response to the growing concern of the medical profession throughout the state regarding assurance of quality patient care under the prepaid health plans (PHP's) being granted Medi-Cal contracts by the state, early this year CMA developed a comprehensive set of performance criteria for such plans. Basic to the 24-point document are requirements that call for PHP's to comply ". . . with the same licensure and professional ethical standards required of other providers of the same services in California, as measured by established professional criteria" and to assure ". . . that medical decisions will be made by qualified medical personnel, unhindered by fiscal or administrative decisions of the governing board."

Conclusion

Medical care in California is complex and varied. So, too, are the dynamic and evolving processes of peer review which the CMA and its component societies are utilizing continuously to safeguard the quality of patient care throughout the state. In CMA's view, this is not a responsibility medicine can delegate. Computerized data banks and norms of care—no matter how sophisticated—can never substitute for the personal involvement of physicians in conscientiously evaluating the care rendered by their colleagues.

CHAPTER III

Government Advocacy

In recent years, the California Medical Association's participation in the legislative process has dramatically increased, as has its involvement with administrative agencies. The last few years have also seen CMA more frequently assuming a positive "advocacy" role in the governmental arena. Particular emphasis is being given to projecting trends and future problem areas as far in advance as possible so that CMA may be in a strong position to take anticipatory action rather than reacting to crises. Still another major trend is intensified CMA involvement at the federal governmental level in cooperation with AMA—based on the premise that the expanding influence of federal proposals and programs on the practice of California physicians must be dealt with at its sources in Washington, D.C.

State Governmental Relations

Currently about one-fourth of proposed state legislation affects the health of the people of California, the environment they live in or the way their health care is delivered. This means that CMA reviews approximately four to five thousand bills introduced at the state level each year. The association takes positions on more than 200 of these bills, based on resolutions adopted by the House of Delegates, on directions from the Council and on advice from appropriate committees. Nearly every CMA committee involves itself in reviewing and recommending legislation in its particular field of expert knowledge, providing a broad, representative base for CMA legislative action.

In all its dealings with proposed legislation, whether initiated by itself or others, the basic test applied by CMA is simply: "Is it good for the patient?" If the answer is "yes," then CMA supports. The association's batting average speaks for itself. Of the more than 150 bills supported in the past two years, over 75 percent were enacted and a number of these were CMA-initiated bills. Of the more than 110 bills opposed by CMA during the same period, all but five were defeated or favorably amended.

CMA tries to involve as many physicians as possible in its legislative decision-making process. For example: every major specialty society is asked to designate two representatives to CMA's State Legislative Commission; county societies are routinely sent status sheets and other legislative material; the legislative committee chairman of each component society receives appropriate material in advance of each State Legislative Commission meeting and is encouraged to provide the commission with the society's viewpoints on specific bills being considered; all county medical societies are invited to send a representative group to Sacramento for an orientation session conducted by CMA.

Communications with the membership as a whole concerning legislative matters is receiving special emphasis. State legislative news is transmitted to every member each three weeks via *CMA News*. In addition, *Sacramento Reports* is sent every two weeks during legislative sessions to the medical leadership throughout California—Councilors, county society presidents and executive secretaries, chairmen of county legislative committees, and presidents of specialty societies.

With implementation of the new unified Department of Health on July 1, 1973, CMA's relationships with the state administration took on new perspectives, but the objective remains the same: to work closely with state officials to try to make their programs reflect as accurately as possible the kind of knowledge and concern about patient care that only the practicing physician can provide. CMA nominates particularly qualified physicians to serve on some 40 consultative bodies at the state level. CMA officers, Councilors and commission and committee chairmen travel to Sacramento regularly to testify at public hearings on state regulations affecting health care, and members of the CMA staff maintain daily liaison with key officials in the various systems of the Department of Health as well as the Department of Corrections, the Department of Consumer Affairs, the California Disaster Office, the Office of Economic Opportunity, the Department of Education, the Department of Finance, the Department of Industrial Relations, the Department of Rehabilitation, the Department of Social Welfare and the Governor's office.

Federal Governmental Relations

With its expanded program in this vital area, CMA now systematically reviews federal legislation, takes definitive positions on bills of particular concern, and to influence the outcome of these measures it communicates these positions forcefully to members of whatever committee of Congress is hearing the bill as well as to the entire California Congressional Delegation. The association's accelerated program of communications with our 43 Congressmen and two Senators involves a continuing exchange of information and views, and takes many forms:

- An annual visitation to Washington during which CMA officers and other key physician leaders personally meet with nearly the entire California Congressional Delegation to keep them apprised of the association's attitudes toward pending or proposed legislation.
- Sponsorship of an annual Administrative Assistants' Conference on Federal Health Legislation consisting of a two-hour meeting with key administrative personnel from each of our Congressional Delegation offices.
- Periodic visits with key congressional committee chairmen, such as Representative Paul Rogers, chairman of the House Subcommittee on Public Health and Environment, to express CMA's support or constructive criticism of specific measures pending before committees.
- Testimony by CMA physician spokesmen before congressional hearings on important health bills.
- Sending important CMA-developed background materials (for example, "Where We Stand on Drug Abuse") to our congressmen to remind them throughout the year that CMA constitutes an authoritative and responsive resource to which they can turn for information and advice as they confront the complex health issues of our time.

This kind of continuous flow of information and personal contact lays a solid foundation upon which CMA can increasingly depend when it wishes to communicate effectively with members of the Congressional Delegation on particularly critical measures coming up for consideration in the House or Senate.

In recent months, CMA has brought its influence to bear on many pieces of federal legislation. Perhaps the most important were: the Health Maintenance Organization bills (CMA has worked for provisions specifying limited funding on an experimental basis with proper evaluation); and the Keogh Retirement Act Amendments (CMA has favored raising the contribution limit and has opposed restrictive contribution limitations on incorporated physicians). The association also took a strong stand on proposed changes in the Federal Rules of Evidence regarding physician-patient confidentiality. Following CMA's communication of its support for retaining the confidentiality of all physician records and all physician-patient communications within the Federal Code, CMA received a letter from counsel for the House Subcommittee on Criminal Justice reporting that the subcommittee had "amended the rules on Privileges, the net effect being to conform with the recommendation of the California Medical Association on Rule 504."

CMA's expanded efforts at the federal level also include active liaison with key officials in the Department of Health, Education and Welfare at both the Region IX and national level, as well as keeping the CMA membership informed regarding important developments on the Washington scene.

California Medical Political Action Committee

California Medical Political Action Committee, (CALPAC) is the bipartisan—voluntary—political action arm of organized medicine in California. The organization is composed of physicians and their wives who are interested in furthering their knowledge of the political world and, in turn, taking an active part in shaping society through participation as interested and concerned citizens. CALPAC provides its members with both the means and the expertise for effective political action on both the state and federal levels. The CALPAC movement arose 12 years ago from the conviction that today's emphasis on political involvement by various segments of the community demands that physicians identify themselves in the political arena by supporting federal and state legislators who are constructively concerned about the delivery of quality medical care.

During CALPAC's first eight years of existence its activities were limited to federal campaigns for the United States Senate and Congress. However, in 1972 CALPAC expanded its activities to include financial support of candidates for state office as well. Its record is impressive. In the 1972 elections, CALPAC and local physicians financially supported 125 candidates seeking office. One hundred and eight, or 86 percent, were successful at the polls. In addition, and perhaps even more important, CALPAC's bipartisan approach is reflected in the fact that 41 percent of these candidates were Democrats and 59 per cent were Republican.

Recently CALPAC has placed special emphasis on organizing various physician candidate support committees at the local level, contributing sophisticated campaign management techniques and assistance to crucial campaigns and through CALPAC's contribution to the American Medical Political Action Committee, enabling AMPAC to help elect medicine-supported candidates to Congress throughout the United States.

In the special elections held during 1973 to fill vacancies due to death, resignation or retirement of state legislators, CALPAC batted 1000. There were six such special elections in California during this past year, four in the State Assembly and two in the State Senate. Based upon the recommendations of local CALPAC members and physician leaders within these districts, CALPAC's contributions in each of these six contests supported winning candidates, including the election of the only current physician legislator in the California Legislature, Doctor Robert McLennan, a Los Angeles general practitioner, to the 38th Assembly District.

CALPAC's membership now stands at a record high of over 7,000 members and it is generally recognized as the most effective state medical political action committee in the country. It is currently mounting a massive membership campaign to assure that medicine can assume a significant role in the 1974 races for Governor, 80 seats in the Assembly and 20 in the California Senate plus 43 in Congress and a U.S. Senate seat.

Conclusion

CMA's many "government advocacy" activities reflect its legitimate concern about the effect of governmental programs—both federal and state—on the ability of physicians to provide the best possible patient care and on the total health care environment for Californians. CMA's role as a governmental advocate both for physicians and their patients will continue to expand in the years ahead.

CHAPTER IV

Improving the Availability of Care

Socio-economic aspects of medical care delivery, as well as quality and availability of care, are primary concerns of the California Medical Association. Through their state and national associations, as well as their county medical societies, California physicians are steadily improving the availability of health care. While the first of seven stated goals of CMA is "to improve the *quality* of health care and services," the second is "to expand the *delivery and accessibility* of medical and health care programs."

This concern about the socio-economics of delivering care is far from new to the association. CMA has a record of pioneering in this field. As early as 1929, the CMA Council studied the feasibility of a plan devised for government to provide care for medically needy persons of limited income. This early proposal, which did not reach the implementation stage, dealt with medical care for people having an income of $2,500 or less. California Physicians' Service, the forerunner of the present California Blue Shield, was founded by CMA in 1939. It was the first plan of its type in the nation.

More recently, CMA sponsored and supported the state bill which enacted the Medi-Cal program "to allow eligible persons to secure basic health care in the same manner employed by the public generally and without discrimination or segregation based purely on their economic disability." However, since its inception in 1966, Medi-Cal has been plagued by problems of political expediency, fiscal restrictions and unrealistic administrative regulations which have actually transformed it into a health care program which restricts patients' access to quality care.

The current efforts of California's physicians to deal with the complex socio-economic aspects of medical care can best be examined by focusing on three key items: cost of care, health manpower, and national health insurance.

Cost of Care

Although physicians' services account for only about 20 percent of all health care costs, California's doctors have demonstrated their constructive concern about keeping the cost of *total* health care as low as is consistent with quality. An important part of the wide spectrum of voluntary peer review efforts described in Chapter II is directed toward "utilization review," a process to assure the propriety of billings to health insurance carriers.

Physicians and their medical organizations are constantly seeking new ways to keep a rein on rising costs. Many of California's Foundations for Medical Care have initiated pilot projects under the Medi-Cal program to attempt to realize savings by having physicians participate on a "prepaid" basis. The Sacramento Foundation has instituted a special "Certified Hospital Admission Program (CHAP)" to cut hospital stays to the shortest feasible length through establishment of norms for hospitalization related to specific medical and surgical situations. The San Joaquin Foundation's Coordinated Medical Utilization program (CMU) assists the physician with each patient, beginning with preadmission screening and continuing to appropriate coordination of discharge planning in order to bring about the most efficient and effective overall utilization of health care resources available. Coordinated Care Organization (COCO), which is sponsored by the Redwood Health Foundation, Sonoma and Mendocino-Lake Foundations for Medical Care, has the objectives of establishing a guaranteed payment program for medically necessary admissions to hospitals, assuring patients necessary care and conserving health care resources. The Medi-Cal Pilot Project of the Fresno and Madera Counties Medical Society compares patient treatment profiles and prior authorization as controls of overutilization to upgrade quality of care and to realize related objectives. The Progressive Review Program of the Stanislaus Foundation for Medical Care is seeking to raise the quality of care available to the community and to lower the cost of providing it. In addition, skilled nursing facility review programs under Medi-Care are being conducted by the San Diego and Riverside county societies, and by District 12 of the Los Angeles County Medical Association. These are only a few of the many examples of innovative efforts at the local level to keep medical care costs at a minimum.

Health Manpower

A recent example of CMA's commitment to assuring the availability of adequate health manpower throughout the state was its support of the 1972 "Health Science Facilities Bond Issue"—designed to provide funds for completion of medical schools and other facilities to train dentists, nurses, public health professionals and other needed health care experts. CMA contributed $5,000 in addition to the equivalent of $25,000 in publicity services. Aided by the profession's efforts and citizens committees, the bond issue passed.

In cooperation with its extremely active Woman's Auxiliary, CMA has expanded its health career recruitment activity in many areas, including wide distribution of "Health Careers Quick Reference Chart" on request.

Since 1968, CMA has awarded scholarships to high school seniors who plan careers in the health sciences through its subsidiary organization, the California Medical Education and Research Foundation (CMERF). In 1973, CMERF awarded a dozen scholarships—four in each of three categories: four-year achievement scholarships for black students, four-year merit scholarships and one-time $1,000 merit scholarships. These scholarships are financed by contributions from Audio-Digest, another CMA subsidiary, and winners are selected by the board of directors of CMERF based on recommendations of component medical societies and in cooperation with the National Merit Scholarship Corporation. Wherever practical, CMA urges medical schools to expand their enrollments and to actively seek out and financially assist interested and potentially qualified minority students who desire education in the health fields.

Studies done by CMA and other organizations indicate that the basic *physician* manpower problem is one of distribution—by geographical location and by specialty. Thus, CMA and its component societies are directing special efforts to increase services in the "inner city" and rural areas, as well as encouraging more physicians to choose family practice as a specialty. Here are a few examples:

- CMA's Physician Placement Service: This program was designed to bring together physicians seeking practice in certain geographic areas and areas needing physicians. Among the most active in the country, the CMA service publishes its *Physician Placement Bulletin* every other month. More than 3,000 copies are sent to California hospitals, county medical societies and medical schools throughout the country. A copy is also sent to each newly licensed California physician and is available to any CMA member on request.
- Component Society Activity: The San Francisco Medical Society works with the Office of Economic Opportunity in bringing medical care programs to the inner city. Fresno County Society has sponsored a rural health care delivery demonstration project in the Firebaugh-Mendota area. Kern, Sacramento and San Joaquin County medical societies, as well as other medical societies, are operating mobile clinics for the treatment of rural migratory workers. The Monterey County Society is the fiscal agent for an innovative rural health project in King City using the health team approach. Other county medical societies—in the ways they find best suited to local needs—are seeing that health care reaches migrant agricultural workers, rural areas and urban ghettos.
- Preceptorship Programs: In the past CMERF has provided grants to the state's medical schools to support students' preceptorships which involve them in programs of family practice and community medicine in rural areas. Recently the CMA Council approved supplementing these preceptorships with a program developed by medical students in cooperation with CMA. The new program, entitled "Student Community Orientation and Preceptorship Education (SCOPE)," will place special emphasis on arranging summer preceptorships in hospitals and clinics in rural and isolated areas.
- New Approaches: Recently, the CMA Committee on Urban Health prepared a comprehensive analysis of "Incentive Criteria for Voluntary Private Practice in Underserved Areas." The committee currently is conducting a survey of California teaching hospitals with the objective of establishing direct contact with new physicians planning to enter practice in low-income areas in order to offer them consultation and advice.
- Family Practice: In October 1973, the Governor signed a CMA-supported bill which appropriates $3.1 million for family practice programs in medical schools and hospitals in California, thus giving a substantial boost to the training of more needed "primary care" physicians.

National Health Insurance

During recent Congressional deliberations on the type of national health insurance which should be made available to the American people, CMA has taken a strong stand on 19 basic principles which must be met if such a program is to be in the best interests of patient care. These points, which reflect CMA's deliberations on health care coverage over a number of years, are as follows:

1. Adequate mainstream health care should be available and accessible to all.
2. All persons should have available a program for securing and retaining adequate coverage.
3. Participation in programs must be voluntary, not compulsory.
4. Freedom of choice for both physicians and patients must be retained.
5. No restrictions should be placed on physicians providing care.
6. Graduated governmental funding for health care, based on level of need, is appropriate.
7. Non-indigent patients should have the responsibility for some financial participation.
8. Universally available programs should repre-

sent a coordinated approach within a pluralistic framework.

9. Adequate standards of comprehensiveness for benefits must be included.

10. Programs should include coverage for services performed on an out-patient basis when appropriate.

11. Physicians should control standard setting in health care programs.

12. True peer review is essential in evaluating care provided, including quality of services and appropriateness of charges; this is an appropriate function of various professional medical organizations but not of government.

13. Accreditation and utilization review committees should be required for institutions participating in health care programs.

14. If certain criteria are met, demonstration and experimentation programs are important; they should involve consumers and local medical societies.

15. The Health Maintenance Organization concept should be implemented on a pilot basis in selected areas before efforts are made nationally.

16. No conflict should exist between any universally available program and coverage provided through employment.

17. Multiple coverage for the same individual or family is inappropriate.

18. Payments to physicians should be on a usual, customary or reasonable basis.

19. Programs should exclude coverage for chiropractic services.

CMA recently reviewed the AMA's Medicredit proposal in the light of these 19 principles. This proposal, as embodied in HR 2222 and S 444, provides for the financing of a national health insurance program by allowing credits against personal income taxes to offset premium costs of qualified private health insurors who offer a specified benefit package. In view of the fact that Medicredit comes closer to complying with CMA's principles than does any other national health insurance proposal and in light of the desirability of a unified approach by organized medicine on this critical matter, the CMA House of Delegates voted last February to endorse this AMA-developed plan. The Medicredit bill had been introduced in January with 126 co-authors, including ten members of the California Congressional Delegation. Since the endorsement action by the CMA House, the association has actively supported Medicredit through its various channels of communications with Congress. Medicredit now has 181 congressional sponsors, including 16 members of the California Delegation—more sponsors than any other national health insurance proposal now before Congress.

Conclusion

Throughout CMA's history, it has been concerned not only about the quality of care, but the availability of care to all Californians. Its past and current efforts attest this concern. Currently, CMA is playing an instrumental role in shaping the kind of national health insurance approach which will evolve from deliberations in the nation's Capitol—an approach which would reflect the medically sound and socially progressive views of California's physicians.

CHAPTER V

Shaping a Healthier Environment

Medical science can point with pride to virtual eradication of most grave contagious diseases and to advances in techniques for the early detection, treatment and cure of heart disease and other killer diseases. It also can be proud that life expectancy in the United States is up 45 percent since the turn of the century—from 46 to 67 years, and infant mortality is down 75 percent in the same period.

However, physicians are increasingly concerned about the rapid rise in incidence of homicide, suicide, automobile accidents, lung cancer and cirrhosis of the liver in California and throughout the nation. These and many other health problems can be traced to social, not medical needs. Their presence indicates serious shortcomings in the knowledge, attitudes, life-styles and living conditions of a significant proportion of our population—factors which ultimately have a far greater influence on the total health of an individual than the medical care he receives once he is sick.

Individually and collectively, the physicians of the California Medical Association are not only acutely aware of the tremendous bearing that personal environment has on total health, but are actively using their knowledge, resources and influence to help overcome the social and behavorial causes of ill health.

CMA Public Education Programs

Foremost among the Association's programs to provide health information to Californians is its "Health Tips" project—now under the sponsorship of CMA's subsidiary, the California Medical Education and Research Foundation (CMERF). More than 300 subjects have been covered by "Health Tips," many of which have been translated into Spanish for California's Chicano population. All of these articles are designed to inform and motivate the individual toward practices which will result in optimal health. Because each "Health Tip" is reviewed by a panel of physicians selected for their special knowledge in the subject being covered, these articles represent a truly authoritative source of public health information.

Launched in 1961 with a mailing to 89 recipients, "Health Tips" now are distributed *on request* to more than 6,000 outlets, including national news services, such as UPI; weekly, daily and farm newspapers; labor and employee publications; business and industrial house organs; educational agencies of the Department of Health, disadvantaged areas, neighborhood health centers, public health clinics and nearly 4,000 key school personnel. County medical societies and schools—kindergarten through universities—use the materials in a variety of ways: duplication and distribution to students and parents in the entire school system; health education course syllabi; health text books; teacher and school nurse education; and health fairs. These articles also are requested by many physicians for use in their offices.

Since the inauguration of "Health Tips," CMA has developed other public health communications programs built around the same carefully authenticated material. Special pamphlets on selected "Health Tips" have been prepared and widely distributed. "Health Tips" information is an integral part of CMA's Radio News Service, which provides a toll-free CMA telephone number California radio stations may call to receive pre-recorded medical news for rebroadcast at a time of their choosing. This 24-hour service is available seven days a week, and currently CMA receives calls from 20 to 25 stations daily.

Shortly public service TV spots based on "Health Tips" information will be available throughout the state. This is a project of CMA's newly created "Committee on Health Education of the Public," which also is launching an extensive survey of public education needs and the adequacy of available sources as well as exploring methods to encourage increased physician involvement at the community level.

County Society Programs

In cooperation with CMA as well as in independent activity, the Association's component medical societies carry out numerous programs which contribute to a higher level of health education throughout the state.

A dramatic example is the "Tel-Med" program, through which taped telephone messages on selected health topics are made available to all members of a community. This new approach, which originated with the San Bernardino County Medical Society in 1972, has been so successful that it is being implemented in San Diego, Anaheim, Long Beach, Fresno and Oakland. Through CMERF, the California Medical Association assisted in funding the first year demonstration of the Tel-Med program, and through the "Health Tips" program, CMA provides much of the material on which these popular telephone messages are based.

The Los Angeles County Medical Association's "Medix" program is in its third season of producing weekly half-hour television documentaries in cooperation with KNXT, the local CBS outlet. These outstanding health education programs, which reach an estimated 800,000 to one and a half million southern Californians every Sunday afternoon, received a regional "Emmy" award during their first year. They also have received important citations from civic and state groups, such as official recognition by the State Highway Patrol and local police for the contribution a "Medix" documentary, "How Drinking Affects Your Driving," made to the alleviation of this problem in Los Angeles during the holiday season. CMERF made a substantial contribution toward funding the 1972-73 "Medix" season.

Health Education in Schools

At the same time that CMA is trying to reach the general population with physician-prepared health education messages, it also is intensively involved in promoting healthful patterns of behavior for California's citizens during their formative years. Thus, CMA works closely with the State Department of Education and, in fact, sponsored and helped to write the "State Framework for Health Instruction" and the administrative guidelines for its implementation. Last month the CMA Council directed the association's Commission on State Legislation to give high priority to the development and passage of a bill requiring health education consistent with the State Framework in all California schools, from kindergarten through high school. The Council also urged the recognition of health education as *survival education* and encouraged individual physicians, county medical society school health committees, the CMA Woman's Auxiliary and others to work with county school offices and school administrators on this basis.

CMA's Committee on School and College Health, which is responsible for developing the programs and concepts described above, has been active for more than 15 years in sponsoring educational programs for professional and lay groups, including school health congresses at CMA's Annual Session.

Combatting Pollution

Although genuine improvement in the health knowledge and attitudes of people throughout the state is the key to a healthier environment for Californians, CMA has determined that the mounting problems of air, water, noise, and land pollution are often most effectively attacked through legislation. Last year alone, CMA supported more than a dozen bills designed to improve the state's ecology.

To deal with the serious problem of air pollution, CMA encourages mass transportation, stringent air pollution standards, use and inspection of vehicle emission control devices, mandatory emission and conversion of fleet vehicles to alternate fuels in high-risk areas, and use of health warning systems to alert area residents when air pollution levels endanger health. Resolutions resulting from a recent Riverside symposium on "Air Pollution and its Effects on Human Health" were considered significant enough to be cited in the September 24, 1973, *Congressional Record*. This important program was sponsored jointly by the Riverside County Medical Association, San Bernardino County Medical Society, the Riverside-San Bernardino Chapter of the California Academy of General Practice, the University of California, Riverside, and CMA.

CMA urges that citizens and state government endorse the "Environmental Bill of Rights" developed in 1970 by an Assembly select committee and supports the concept of a central state agency for environmental quality. Among other anti-pollution measures supported by CMA are: research and action to prevent contamination of our oceans and waterways; adequate sewage and solid waste disposal; use of recyclable and biodegradable products; rat control; maintenance of recreational areas; and research funding to assure that nuclear energy development takes environmental factors into consideration. CMA's active Committee on Environmental Health has spearheaded these and many other efforts.

Other CMA Programs

CMA has established numerous committees whose activities are geared to helping solve specific social problems underlying ill-health and premature death. Some notable examples are the Committee on Mental Health, which recently has been involved in evaluating approaches to the study of causes of violence; the Maternal and Child Care Committee, which is currently engaged in a program designed to reduce perinatal mortality, stressing the need for health education and the important part played by personal nutrition; and the Committee on Automotive and Traffic Safety, which works closely with the Department of Motor Vehicles and the California Chapter of the National Safety Council to help prevent accidents on California highways.

CMA's Committee on Alcoholism and Other Drug Dependence has pinpointed alcoholism as the most deleterious drug problem in our society. This committee has been responsible for development of CMA's widely-used document, "Where We Stand on Drug Abuse," which urges not only intensified physician training in the techniques of diagnosis and treatment associated with drug abuse, but the establishment of sound, comprehensive treatment programs in which the whole community actively contributes to the social readjustment of the patient.

Conclusion

All in all, the California Medical Association has more than a dozen committees contributing to the public education and protection efforts described in this chapter. CMA's commitment to health is a total one, and thus it is deeply involved in bringing the knowledge of its members to bear on overcoming the social and behavioral causes of ill-health, with the goal of shaping a healthier environment for all Californians.

CHAPTER VI

Serving the Membership

All of the activities and accomplishments described in this seven-chapter article serve the members of the California Medical Association. Among them are a number of vital CMA services designed specifically to benefit the individual member directly, as distinguished from those programs which benefit him indirectly by providing a collective means for California physicians to lead the way in meeting the full spectrum of health care challenges: scientific, educational, socio-economic, environmental, political.

Information Services

Through his Association, the CMA member receives two major publications containing information on a wide range of subjects useful to him in his practice and in his activities as a physician-citizen. First, of course, is CALIFORNIA MEDICINE, soon to become THE WESTERN JOURNAL OF MEDICINE. Acclaimed as one of the nation's finest scientific journals, this monthly publication attracts contributions from leaders in medical science and features "Epitomes of Progress"—short reports on recent advances in all specialties. It also has complete listings of continuing medical education opportunities.

CMA's second membership publication is *CMA News,* which reaches each member physician every three weeks, keeping him up to date on activities of CMA and AMA, County Societies and their foundations, allied health associations, and providing news of legal actions, and meetings of interest. As a regular feature of *CMA News,* "CMA Advocate" provides members with the current status of health legislation at the state and federal levels, as well as other developments in Sacramento and Washington.

Occasionally throughout the year, CMA leaders deem an issue to be so urgent as to warrant a special letter from the President to all members—a recent report on CMA and AMA actions concerning the Phase IV wage-price controls is a case in point.

Other publications, such as *Medical Executives Memo,* a capsulized weekly news sheet, and *Socio-Economic Reports,* a monthly research publication, are sent to county society leaders and other members on request. Although the mailing list for these publications is limited, much of the information is reprinted by component medical societies for their entire membership.

Still other major channels through which CMA communicates with its members are: *Statewide Meetings,* such as CMA's Annual Session, its Component Society Leadership Conferences, meetings of chiefs of medical staffs and conferences on special issues; *Leadership Visitations* by CMA's President and President-Elect, who travel to the majority of California's 40 medical societies to maintain two-way communications with the "grass roots" accompanied by CMA Councilors and field staff representatives, whose job it is to maintain continuous contact with county societies.

Public Relations Services

The Association has a rapidly expanding public relations program designed to improve public awareness, understanding and support of its members' views and contributions. In addition to accelerating its ongoing efforts to inform the public of the constructive action programs of California physicians, CMA has recently launched a number of projects. CMA's continuous public relations program includes an average of three press releases each week and two radio news tapes a month, public presentations by our physician leaders and day-to-day contacts with representatives of all forms of media. Among CMA's newer approaches to establishing an informed public opinion base are the following:

TV Newsfilms—This exciting television effort, in which one- to three-minute action films are prepared on major health issues and the involvement of California's physicians in them, has been extremely well received by news programmers throughout the state. A new film is distributed monthly to some 25 television stations throughout the state and usually is aired by three-quarters of them. The films are shown during prime time —either the 6:00 p.m. or 11 p.m. newscasts which reach 70 percent of California households having TV sets. If CMA were to purchase this time for a year, the cost would run well over $100,000. Instead, broadcasters have picked up the films because they are newsworthy and professionally prepared.

Coordination of Media Efforts—Last year, CMA received AMA's first annual award to a medical society for its three-pronged media approach to a given issue. On important CMA stories, press releases are coordinated with supportive coverage through the CMA Radio News Service and a TV Newsfilm—thus creating greater public impact.

Media "Backgrounders"—To present medicine's point of view in a positive manner, CMA's President and other leaders have begun holding news media background briefing sessions throughout the state for reporters and science writers. These "backgrounders" are being well-attended and well-received. While the intent was to provide background information for the media's use in future stories, the meetings have generated considerable "bonus" news coverage. At each of these sessions, position papers based on CMA policies on topics of public interest are distributed to media representatives. These are the same position papers published in this special issue of CALIFORNIA MEDICINE.

Patient Messages—Last July, CMA began a pilot project through which a brief patient message in the form of a "stand-up" tent card was mailed to each member via *CMA News* for placement on the magazine table in his waiting room. Written in a personal style appropriate to the physician-patient relationship, the first three messages covered physician-patient confidentiality, peer review, and quackery. The project is currently being evaluated by CMA's Commission on Communications to see if it has been an effective tool for physicians.

Professional Services

To assist the individual member, CMA offers or sponsors a great variety of programs of economic importance to physicians:

- Development and updating of the *Relative Value Studies,* a means of accurate communication between individual physicians and insurance carriers, providing for specific identification of medical services. CMA's *RVS* is widely used throughout the country and is the basis for AMA's *Current Procedural Terminology.* It also has been accepted by the Social Security Administration for the use of code numbers and nomenclature under the Medicare program. A free copy is provided to each CMA member.
- A flexible investment program which meets the requirements of the Keogh Act, with nine investment options, including eight different mutual funds, an annuity plan, or a combination of these to meet the individual member's personal needs. Pending federal legislative developments, CMA plans to make further improvements in this program.
- A special term life insurance program for members of the association, which combines high limits, low costs and ease of enrollment.
- A disability income program, which provides up to $1,500 monthly disability income payable for the insured's lifetime, if totally disabled due to injury, or to age 65, for illness disability.
- An accidental death and dismemberment policy, which offers CMA members a "loss of use" benefit in addition to high limits and low premiums.
- The Physicians' Benevolence Fund, through which CMA provides short-term assistance for physicians and their families in times of economic need. The fund is maintained by allocating a portion of each member's dues plus generous contributions from the CMA Woman's Auxiliary and others.

CMA's Commission on Member Services is constantly looking for new ways in which the association can be of direct service to physicians. Recently, the Council approved Commission-recommended proposals to make an excellent automobile leasing plan available to members where desired and to consider development of educational group tours in conjunction with CMA's continuing medical education program. CMA is currently preparing a legal-office-business manual for use by physicians and is developing a comprehensive catalogue of all services and materials which are available to assist component medical societies and individual physician members.

Special Services: Professional Liability

Space does not permit description of all the special services CMA makes available to its members, but its continuing and extensive efforts to alleviate the serious professional liability problems which face physicians deserve particular attention. The association is attacking the professional liability situation on many fronts.

- A reference book, *Professional Liability . . . Selected Medical-Legal Information for Physicians,* was prepared by CMA and distributed to every member. It is a basic reference for background information and contains sample consent and release forms and letters designed to assist the physician in his practice.
- A demonstration project in patient arbitration, co-sponsored by CMA and the California Hospital Association, is seeking to develop a sta-

tistically accurate evaluation of the concept of arbitration in professional liability.

- CMA's malpractice legislative program has brought about the passage of ten important bills dealing with *res ipsa loquitur;* statute of limitations; confidentiality of medical staff, medical society and medical foundation committee proceedings; and the cost bond measure, which required a deposit of $2,500 as a bond in an action brought against a physician for punitive damages. Legislative proposals affecting contingency fees, measurement of damages and disclosure are being actively pursued.
- Legal advice on informed consent, as it affects physicians under the recent State Supreme Court ruling, is continually conveyed to all members through special mailings, organized discussions, and tape-recorded summaries.
- In addition, CMA conducted an actuarial analysis of the liability situation, has sponsored regional professional liability workshops, urged the AMA to develop a specific department to provide a national focus on professional liability problems, is actively preparing CMA testimony for hearings of the Assembly Select Committee on Malpractice, and provides assistance to component medical societies on request.

Conclusion

CMA's programs are created by and for California's physicians. All members are urged to draw upon the resources the association offers and participate in the formulation of CMA's policies and programs. Through member services, the California Medical Association and its county societies are improving the environment in which our state's physicians practice and in which their patients receive care.

CHAPTER VII

Planning and Evaluation

As health care challenges have proliferated, the California Medical Association has become increasingly aware that its limited resources must be deliberately channeled by priority into programs which are the result of careful planning and are subject to regular and systematic evaluation as to their relative importance, whom they are important to, and how they relate to the purpose of the association.

Concrete testimony to CMA's concern with the *planning process* is found in the association's continuing effort to approach the complex task of establishing specific organizational goals and objectives. A *goal* is a condition to be achieved that is crucial to the long-range success of an organization. *Objectives* are the markers along the path by which a goal is to be reached. They include the steps that are taken day-to-day and year-to-year to keep the organization relevant, cohesive and moving in a predetermined direction toward its goals. Because objectives are specific progressive targets, they provide a means to measure at any time not only the accomplishments but also the effectiveness of an organization. Both goals and objectives must be realistic and attainable. But because our society and the demands and needs of any organization are subject to constant change, failure to reassess established goals can only result in ineffective activity.

Since 1967, when CMA's first goals and objectives were outlined, the association has reassessed and refined its goals on five occasions. Today, CMA activities are increasingly geared to reaching the following seven goals:

1. To improve the quality of health care and services.
2. To expand the delivery and accessibility of medical and health care programs.
3. To present medicine's interest to government and other organizations.
4. To strengthen CMA and its component societies as a statewide organization.
5. To develop better informed public attitudes toward physicians and organized medicine.
6. To improve the public's health knowledge and practices.
7. To expand direct member services.

Within the context of these basic goals, CMA establishes objectives and decides on priorities to guide the allocation of time, money and other resources of the association. These decisions are often extremely difficult ones, and while all CMA commissions and committees have been involved in making annual projections of their respective objectives since 1970, CMA has a number of organizational entities specifically designed to make major contributions to the overall planning effort.

The Bureau of Research and Planning

One of the first visible affirmations of CMA's belief in planning was the establishment of its unique Bureau of Research and Planning in 1958.

At that time, there was no other single organization or agency—government or private—sponsoring research of any magnitude directed at seeking the kind of factual, unbiased information which could help CMA reach sound conclusions and develop constructive, farsighted policies. The Bureau has filled this vital need by laying a firm foundation of research for more purposeful planning by CMA.

The scope and significance of the Bureau's work is indicated in a brief review of some of its recent projects: a three-part *Socioeconomic Report* on the use and misuse of death statistics, with particular emphasis on infant mortality, longevity and morbidity statistics; a three-year census study of continuing medical education, which provided data on physicians' patterns of involvement in formalized programs of continuing medical education; reports on occupancy trends, health insurance coverage and hospital length-of-stay patterns; a series of *Socioeconomic Reports* on physician supply in California, with analysis of trends that have taken place in the past ten years, discussion of distribution and the degree to which a shortage exists and development of data concerning costs of providing care in the private versus the public sector.

The Bureau continuously maintains information on subjects such as physicians' fees, multiphasic health testing programs, computers in medicine, health care delivery patterns, health insurance coverage, health manpower, cost of care and other vital subjects.

An important new activity initiated by the Bureau this fall is the "CMA Member Opinion Poll." The first two questionnaires, mailed to a random sample of the membership, attempt to evaluate the degree to which CMA's goals, policies, activities and services represent members' expectations and desires. This additional way of obtaining direct input from members promises to be a valuable tool in setting future directions for the association.

The Committee on the Role of Medicine in Society

By presenting realistic and frank discussion of the issues that confront medicine today, the Committee on the Role of Medicine in Society seeks to help shape the role of the physician and medical practice in the years immediately ahead. Six comprehensive progress reports have been published by the Committee since it was established. Its most recent report was, "The Physician and His Practice, 1980-2000."*

In addition to studying the effect of social change on the future role of the physician and making recommendations for positive responses to change, the committee has made an outstanding contribution to the future of the organization by actively involving medical students in CMA's activities. Students representing each of California's medical schools participate in this committee's deliberations, and it has been instrumental in gaining student participation on 55 other CMA commissions and committees. The committee also has arranged for students selected by their peer groups at each medical school to attend AMA conventions and the CMA House of Delegates, and has initiated production of a student-written and edited newsletter to convey organized medicine's message to all California medical students.

These and other activities culminated in the 1973 CMA House of Delegates' making a decisive investment in the future of the organization —the creation of an active CMA membership category for California's medical students as well as its residents and interns at reduced dues levels, with voting privileges and representation in the House.

Committee on Organizational Review and Planning

With the growth in size, activities and influence of the CMA during the past decade, it seemed imperative that the structure and functions of CMA as they relate to its goals be reviewed and defined. In 1966, the Committee on Organizational Review and Planning was created as a special committee of the Council to meet this need. The committee was further instructed:

- To review and analyze problems in whose solutions CMA should lead and participate.
- To review the structural organization of the CMA; and
- To plan for and propose changes in CMA organizational structure to improve its overall functioning.

Currently, this committee is deeply involved in a detailed and comprehensive analysis of CMA's progress and plans in relation to its seven basic goals—including specific measurable objectives, priorities, timetables, commission-committee structure and assignments, and criteria for evaluation—and the development of a long range planning process which offers great potential as an organizational tool.

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*The physician and his practice: 1980-2000—Sixth Progress Report of the CMA Committee on the Role of Medicine in Society. Calif Med 116:71-95, Apr 1972.

Council Planning Workshops

Because the Council of the CMA is the group responsible for implementing policy set by the House of Delegates and dealing with the myriad interim problems that arise between annual meetings, Council members have felt that they need to set aside time for thoughtful, creative planning. Since 1968, the Council has held five "planning workshops," during which CMA's goals and objectives—both past and present—have had their genesis. Perhaps the extent of the Council's commitment to the planning process is best expressed by quoting a brief portion of its report to the 1972 House of Delegates:

> We believe that CMA's various programs must be subjected to intensive scrutiny from the standpoints of priority, current relevance, progress toward achievement and appropriate involvement at the proper membership level. Continual program analysis and performance review are mandatory to help us work more effectively on fewer and more significant tasks. If needs and problems determine organizational structure and not the reverse, we have a real chance to streamline the Association, focusing its activities on the most important and appropriate objectives.

Conclusion

The activities and accomplishments described in the first six chapters of this article testify to the goal-oriented growth which the California Medical Association is achieving. The thousands of physician-hours devoted to CMA programs are resulting in healthier, safer Californians and helping to keep our state one in which a physician can be proud to practice the art and science of medicine. And CMA's commitment to continuous organizational self-renewal through planning and evaluation assures that this medical association will meet future challenges with even more strength and determination.

Refer to: Elmendorf T: The California Medical Association—From the past to the future. Calif Med 119:38-41, Dec 1973

From the Past to the Future

THOMAS ELMENDORF, MD
President, California Medical Association

DURING THE LATTER eighteenth century and early nineteenth century in California—the Spanish and Mexican periods—the practice of medicine largely was left to a handful of military surgeons and the mission padres. But as the young United States began to move westward, private physicians from the East accompanied the other pioneers and established themselves and their families in California. Until gold was discovered in 1848, the development of medical practice in California was gradual and generally well-ordered.

The Gold Rush, however, brought chaos. In less than three years an estimated 250,000 people descended on the established population of 14,000. In the confusion of the mass immigration, it was often impossible to distinguish the trained and qualified physician from the self-styled one. For every competent doctor practicing, there were numbers of imposters and quacks. A prominent early physician, Dr. Thomas M. Logan of Sacramento, observed: "In the whole history of the immigration into this vast continent, from the first landing of our forefathers on the Atlantic border, down to our last halting-place on the Pacific Ocean, there has never occurred such an amount of suffering and calamity as has accrued since the discovery of gold in California."

To the legitimate physicians, it seemed obvious that some basis of practice should be established—as well as a means of furthering the exchange of information and experience. Under the leadership of Dr. J. D. B. Stillman, the Medico-Chirurgical Association of Sacramento was formed on

Dr. Thomas M. Logan, prominent California physician and major organizer of the state medical association.

Reprint requests to: Division of Professional and Public Relations, California Medical Association, 731 Market Street, San Francisco, CA 94103.

May 2, 1850. The purposes of the organization were stated as "the cultivation of science; the promotion of honor, dignity and interest of the profession, and the separation of the regular from the irregular practitioners." Similar organizations soon followed in such major cities as San Francisco and Los Angeles.

By 1856, a movement had begun to form a state medical organization. At the call of the Sacramento Medical Society, various delegates met in Sacramento on December 11, 1856, and from this convention ultimately resulted the California State Medical Society. At a second meeting on March 12, the infant society elected Dr. B. F. Keene of El Dorado County as its first president.

In its early days, due to the difficulties of travel, the state society was almost entirely a Northern California organization. Of the 195 members of the society in 1873, all but seven were from north of the Tehachapi mountain range. The counterpart organization in the southern part of the state was the Southern California Medical Society, founded in 1888.

With the reorganization of the state society, which followed that of the American Medical Association in 1901, the present structure was established. Based on the national system, the California Medical Association today is a statewide organization composed of 40 component county medical societies.

Dr. Benjamin Franklin Keene, elected first president of the California State Medical Society in 1856.

From its founding, the organization has given priority to establishing and maintaining high medical standards in California. At the urging of the societies' leaders, the State Department of Public Health was organized in 1870, and the Medical Practice Act was approved in 1876, establishing California's first examining boards for licensing of physicians.

A Willingness to Pioneer

In 1902, the official journal of the association was among the first medical publications in the nation to begin careful review of proposed advertising and to refuse advertising space to products of questionable medical value. In more recent times, CMA strongly supported the Short-Doyle Act, which helped modernize California's approach to caring for the mentally ill. The concept of eye banks was pioneered by CMA in 1947, after the country's first corneal transplant was done in San Francisco. In 1957, the CMA sponsored the first and the model law legalizing the right of an individual to donate his body or part of it for transplant—at a time when human organ transplants were still in the realm of medical research.

In 1964, CMA was one of the primary architects and supporters of the bill which created the Medi-Cal program of health care for the poor. One of the stated objectives of this law is "to allow eligible persons to secure basic health care in the same manner employed by the public generally and without discrimination or segregation based purely on their economic disability." Since the beginning of this program, CMA has worked long and hard in an attempt to keep Medi-Cal committed to this principle. We have offered a number of plans for its improvement. And in another approach, in 1971 CMA waged a court action on behalf of the poor to restore administration cutbacks in the Medi-Cal program, which were producing discrimination and hardship. The ruling of the court stated that the Department of Health Care Services had acted illegally in restricting Medi-Cal services and declared "the regulations . . . invalid and enjoins their application or enforcement hereafter."

In medical and health science, California has made impressive progress. Its two pioneering medical schools have mushroomed into eight, two schools of public health have come into being, and many other professional schools of high caliber have developed. The CMA has supported this progress. In 1970, we gave both financial aid and service in an all-out (though then unsuccessful) effort in behalf of a proposition on the state ballot for a bond issue which would have provided funds for the completion of three medical schools and facilities to train dentists, nurses, public health workers, and other needed health care professionals. In 1972, we gave similar support to the new—and successful—health facilities bond issue.

Innovations

In 1962, the CMA established the first Scientific Board to be found in any medical association. This was done in response to a recognized need for the organized profession to strengthen its capability to improve the scientific quality of the health care rendered to patients. The Scientific Board is composed of representatives from the scientific sections of the CMA and an equal number of representatives from scientific specialty societies which have been recognized for this purpose. The scope of activities of the Scientific Board, and the number and caliber of persons involved, has now placed the CMA in an unusually authoritative position with respect to the scientific aspects of health care.

In recognition of the progress in medical science which has taken place since World War II, the CMA has steadily increased its involvement in the continuing education of physicians—whether or not they are members of the CMA. For many years it has sponsored regional postgraduate institutes, circuit courses in rural areas and extensive annual scientific sessions. In 1970, we launched a pioneering program of "certification" for all physicians who participate in a minimum of 200 hours of continuing education in a three-year period. This program also provides specific mechanisms for accreditation of the continuing education courses and programs themselves, acting to improve their quality and their effectiveness as a means of improving patient care.

The socioeconomic problems of delivering medical service of high quality to all who need it have increasingly occupied the energy and resources of the California Medical Association. During the depression of the 1930's, the CMA, backed by the physicians of California, created the California Physicians' Service which was to become the first Blue Shield Plan and a model for the rest of the nation. As the health insurance concept grew and spread it became evident that some means was needed to define and determine values for a wide variety of physicians' services. The CMA developed the *California Relative Value Studies,* which has now undergone a number of revisions, each of which was adopted widely in other parts of the country. The most recent revision is the basis for the Current Procedural Terminology (CPT) adopted by the American Medical Association.

The Finding-Out Process

Many years ago the CMA, recognizing the need for more, and more accurate, information on quality and cost in health care, established the first socioeconomic research arm in any medical society, the CMA Bureau of Research and Planning. This CMA activity has achieved national distinction and its authoritative monthly Socioeconomic Reports are read widely and with great interest.

Peer review has been pioneered by the doctors of California. California Medical Association and the county medical societies have standing peer review committees—hundreds of experienced physicians who volunteer their time to review the quality and appropriateness of the medical care other doctors provide for their patients. Among many other aspects, I might mention the work of hospital tissue committees in reviewing indications for surgical operation, the survey teams that review hospital medical staffs and the committees reviewing medical care in nursing homes.

In addition, the role of peer review has been expanded into the field of cost control—evaluating the medical charges made by a physician. A third and related objective of peer review activities is to promote effective utilization—to discourage, for example, unnecessary laboratory tests or excessively long stays in hospital. Also, on the patient's behalf, to deal with under-utilization, which obviously can be just as serious for the patient's health.

It also should be noted that the medical profession is actively seeking ways to eliminate health care deficiencies that do exist, without sacrificing the already high level of medical care we have achieved in this country. Many new and innovative approaches to the delivery and financing of medical care are being studied in California—and throughout the nation.

The California Medical Association feels that the "pilot project" is a particularly useful tool in this regard. This is a method of judging the effectiveness of new approaches through a controlled, small-scale trial project. For example, a San Joaquin pilot program is studying whether the state's Medi-Cal program for the poor can be improved by putting payment for providers' services on a prepaid basis. A premium rate per recipient per month has been established to cover all physicians' services within a specific geographic area. A system of reviewing costs and utilization is built into the program. The project hopes to determine whether a greater percentage of the eligible persons would be seen by a greater proportion of physicians under this approach. If so, then this method would assure quality medical care and—at the same time—perhaps supply it for less cost.

Efforts to Spread Good Medical Care

In our efforts to make good medical care available to everyone in the state, we are using a variety of approaches, and I will cite just a few examples.

CMA maintains a Physician Placement Service created specifically to place physicians in locations where medical services are needed. We all have heard references to a "physician shortage" in this country—but recent information indicates that solving our health manpower problem is more a matter of achieving better distribution of physicians than of finding new ways to increase the overall number of physicians. According to the recent President's Manpower Report to Congress, by 1980 there will be about 440,000 physicians in this country—enough to eliminate any overall doctor shortage. This figure represents a predicted ten-year increase of 120,000 physicians, using present educational approaches.

The foundation for medical care is still another approach being taken by the medical profession—and one in which California has led the nation. These foundations are non-profit organizations of doctors sponsored by local county medical societies. They are concerned with the development and delivery of quality medical services at a predictable cost, whether it be privately or publicly financed.

These are a few of the approaches being taken by the medical profession in California to improve our health care. We have identified the problems as being concerned with access to care, quality and cost of care. And we have tackled these problems voluntarily, without simply turning them over to Washington for attempted solution through federal programs—which too often are unreasonably expensive and accomplish too few of their stated objectives.

No one has a deeper concern about health care than the medical profession. Practicing physicians live with their patients' health problems and illnesses every day of the week. The California Medical Association is fully aware that the present health care system contains significant deficiencies. Some people who cannot afford adequate care go without it—because it simply isn't as available to them, because they don't know how to obtain it, or because they lack education to use what is available. Government health programs promise full health care, but don't budget enough to provide it. Furthermore, catastrophic illness can hit any income level. Even those with incomes well above poverty levels can be wiped out financially by a prolonged family illness. In addition, certain people living in remote rural areas or in urban ghettos have no readily available access to the health care system.

We will continue our efforts to improve health care, our experimentation, our pilot projects. We firmly believe there is no single, simple solution to the widely varied health difficulties of California—and of the nation. Therefore, we plan to continue our search for improved methods in the delivery and financing of health care, our commitment to good health care for all Californians. This is the role—and the obligation—of a state medical society as we see it.

Refer to: Where we stand—California Medical Association Position Papers on abortion, acupuncture, chiropractic, confidentiality, cost of care, drug abuse, environmental health, health education for the public, health in the United States, health quackery, health maintenance organizations and prepaid health plans, health manpower, national health insurance, physician's assistants, physician unions, professional standards review organizations, and quality medical care. Calif Med 119:42-59, Dec 1973

Where We Stand

To serve the interests of members and to function in the public interest, the California Medical Association must set policies and take positions on current issues affecting the health care of Californians. These policies then guide the activities of the Association in fulfilling its leadership role and its responsibility to the public.

Delegates, elected by the membership of CMA's component medical societies, meet annually to deliberate and determine the policies and courses of action for the Association. Between meetings of these Delegates, the CMA Councilors, elected by their district membership, implement the directives of the Delegates and set interim policies. By this democratic process, the membership governs the CMA.

Association members must be informed if they are to participate effectively in the affairs of their medical organizations. To disseminate better understanding of CMA's activities, position papers on current issues have been developed. They are based on House of Delegates resolutions and Council actions. Entitled "Where We Stand on Medical and Health Issues," these papers represent the current policy positions of CMA. Each paper is annotated to give the reference source of the policy actions.

As with any organization, CMA policies are subject to timely revision. When policies are amended or new policies are adopted, new papers will be developed.

Following are CMA position papers on:

- ABORTION
- ACUPUNCTURE
- CHIROPRACTIC
- CONFIDENTIALITY
- COST OF CARE
- DRUG ABUSE
- ENVIRONMENTAL HEALTH
- HEALTH EDUCATION FOR THE PUBLIC
- HEALTH IN THE UNITED STATES
- HEALTH QUACKERY
- HEALTH MAINTENANCE ORGANIZATION AND PREPAID HEALTH PLANS
- HEALTH MANPOWER
- NATIONAL HEALTH INSURANCE
- PHYSICIAN'S ASSISTANTS
- PHYSICIAN UNIONS
- PROFESSIONAL STANDARDS REVIEW ORGANIZATIONS
- QUALITY MEDICAL CARE

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Abortion

THE TERM ABORTION refers to "any procedure performed primarily for the purpose of terminating a pregnancy."

Today there is a wide divergence of opinion among lay persons and members of the medical profession on the subject of abortion. Is it ethical and moral for a woman to have an abortion if it is not strictly necessary for her physical or mental welfare? Is it ethical or moral for a physician to perform an abortion? Who has the right to make the decision? And at what point in the pregnancy? Although such questions remain either unresolved or a dilemma for many, abortion laws—once considered inviolable—have been liberalized in a number of states. In recent years, though public and legal opinion has moved in the direction of making abortion decisions a matter between physician and patient, the issue is still often hotly debated.

In January 1973, the United States Supreme Court lifted all restrictions on a woman's right to a physician-performed abortion during the first three months of pregnancy, saying that during the first three months, the decision to have an abortion lies with the woman and her physician; the woman has a "right of privacy" in which the State cannot interfere. It added that "the abortion decision in all its aspects is inherently and primarily a medical decision, and basic responsibility for it must rest with the physician." The court stressed that a physician cannot be required to perform an abortion if against his judgment or moral principles. The Supreme Court decided that states may "regulate the abortion procedure in ways reasonably related to maternal health" beginning with the fourth month of pregnancy.

CMA's Position

The California Medical Association believes that abortion is a medical procedure governed by the Medical Practice Act and, as such, is a matter between the patient and her physician. In 1970, the California Medical Association's House of Delegates voted to adopt this policy, adding that abortion should "be governed by medical standards of sound clinical judgment and informed patient consent, according to the merits of each individual case[1]." As any other medical procedure, abortion should not be performed if it would be detrimental to the best interests, physical or mental, of the patient. Good medical practice indicates that abortion should not be performed after the 20th week of pregnancy.

CMA strongly opposes any factor that might lead patients into the hands of criminal abortionists, and therefore believes that abortions should "be performed in hospitals approved either by the Joint Commission on Accreditation of Hospitals or the California Medical Association Medical Staff Survey, or in appropriately equipped outpatient facilities demonstrating adequate mechanisms for local peer review.[2] Availability of such facilities to pregnant women seeking abortions decreases the number of illegal abortions and the risk to the patient's health.

Realizing that some physicians may disagree with CMA's position on abortion, whether for moral, ethical, medical or psychiatric reasons and acknowledging the wide spectrum of opinion on the subject, CMA believes that—as with any medical procedure, abortion should never be performed "on demand[3]." CMA holds that no physician may be required to violate his own conscience by performing an abortion, nor should any member of the health team be required to assist with an abortion, nor should a hospital be required to permit an abortion in violation of moral principles to which it is dedicated. The alternatives offered to members of the medical profession who oppose abortion are: "(1) to try to remove the stigma attached to pregnancy, (2) to provide emotional support to the patient during pregnancy, (3) to help in adoption, (4) to offer advice regarding future contraception or sterilization or (5) to withdraw from the case if the patient insists on an abortion, so long as the withdrawal is consistent with good medical practice[4]."

In all abortion cases, CMA urges the physician to provide pre- and post-abortion counseling and supports policy that recommends family planning counseling.[5]

CMA has established a standing committee "to consider the response of the medical profession to the evolving scientific, technological and philosophical trends in our society as they affect human life[6]." This committee has helped to evaluate policy on abortions, and is delving into other issues which concern society and its relationship to the medical profession.

REFERENCES

"HDR" refers to CMA House of Delegates resolution
"CA" refers to CMA Council action

1. HDR 9-70; HDR 8-73; CA 5/1/70
2. HDR 189-73
3. HDR 9-70; HDR 8-73; HDR 9-73
4. HDR 9-73; HDR 9-70; CA 6/11/71
5. HDR 9-73; CA 7/28/72
6. HDR 8-73

Acupuncture

THE RENEWED FOCUS of attention on mainland China during recent years has brought with it an interest in the practice of traditional Chinese medicine, particularly acupuncture. This technique, whose history dates back more than 1,000 years, involves the insertion of thin needles into various points of the body and claims results as an anesthetic, as a means of relieving pain, or as a cure for various ailments. After the acupuncture needles, which are about three inches long, are inserted one-quarter to one-half an inch into the skin, they are twisted, vibrated or moved up and down depending on the treatment. Chinese practice teaches that there are up to 1,000 acupuncture or sensitive points on the body's "meridians" where two or more needles can be inserted to produce the desired results.

CMA's Position

The California Medical Association has urged a scientific evaluation of acupuncture "because of intense interest in the technique, which may have potential value in the relief of pain[1]." This action was followed by the introduction and passage of state legislation at the request of CMA which makes possible scientific studies of acupuncture and other forms of traditional Chinese medicine.[2] The law allows a non-physician to perform acupuncture, under a physician's supervision, in a California medical school for the purpose of scientific research. (Since acupuncture requires piercing of the tissues, it falls within the classification of "the practice of medicine" and therefore legally can be practiced only by licensed physicians and surgeons.) More recently, CMA opposed additional legislation authorizing expanded use of acupuncture in the state, pending receipt of a progress report on medical school evaluations of the technique.[3] Recognizing the widespread interest in acupuncture, the California Medical Education and Research Foundation, a non-profit subsidiary of CMA, has initiated a grant program to stimulate scientific investigation of the ancient technique in California's eight medical schools and the Charles R. Drew Postgraduate School of Medicine in Los Angeles.

REFERENCES

"CA" refers to CMA Council action

1. CA 5/19/72
2. CA 7/28/72
3. CA 1/5/73

Chiropractic

CHIROPRACTORS DISAGREE among themselves on the definition of chiropractic. One group, known as the "straights," adheres basically to a rigid definition, holding that the sole route to restoration of health, no matter what the problem, is through manual manipulation of the spine. A second group, known as the "mixers," advocates the use of such modalities as heat, light, water, electricity, vitamins, colonic irrigation and other physical and mechanical adjuncts, in addition to spinal adjustments. Each group is represented by a national organization.

The chiropractic concept of disease is unsupported by scientific facts, and causes of infections and other diseases cannot be explained by the chiropractic theory that disease is caused by a "subluxation" (partial dislocation) in the spinal column. Many chiropractors claim to be able to cure everything from headache to cancer by spinal manipulation—although medical research has proved their claims impossible.

In regard to education, a study by the Department of Health, Education and Welfare notes ". . . irrespective of its theory, the scope and quality of chiropractic education do not prepare the practitioner to make an adequate diagnosis and provide appropriate treatment." Furthermore, no chiropractic school is accredited by any nationally recognized educational accrediting agency in the United States and chiropractic education is provided for the most part by chiropractors without a degree from an accredited college.

Forty-eight states impose license limitations on chiropractic, prohibiting chiropractors from prescribing drugs and performing surgery. Two other states—Louisiana and Mississippi—do not issue even limited licenses.

The scientific community—including the medical profession—regards chiropractic as an unscientific cult, the largest group of unscientific practitioners in the United States.

CMA's Position

CMA has emphasized repeatedly that chiropractic is an unscientific cult and that its practitioners lack the training and background to diagnose and treat human disease. Chiropractic is not a practice of medicine[1] and constitutes a hazard to health in the United States because of the substandard and unscientific education of its practitioners and their rigid adherence to an irrational, unscientific approach to disease causation. A patient who relies on chiropractic may delay proper medical care until serious and irreversible damage occurs. CMA pursues public recognition of this principle through public education campaigns and works to discourage chiropractic and other health cultism in all ways.[2]

The California Medical Association strongly disapproves of the payment of Medi-Cal, Medicare, Workmen's Compensation, Veterans Administration and other funds to chiropractors.[3] In addition, CMA has worked against inclusion of chiropractors in any insurance contracts.[4]

REFERENCES

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"CA" refers to CMA Council action

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Confidentiality

Patient-Physician Communications, Patient Records

FROM THE EARLIEST of times, confidentiality between doctor and patient has been considered a sacred trust, an essential aspect of the patient-physician relationship. An oath taken by Hindu physicians, 1,500 years before the birth of Christ touches on the subject. And the "Oath of Hippocrates," dating back more than 2,000 years, states: "Whatever, in connection with my professional practice . . . I see or hear in the life of men which ought not to be spoken of abroad, I will not divulge, as reckoning that all such should be kept secret." Similarly, Article 9 of the American Medical Association's "Principles of Medical Ethics" deals with this matter of confidentiality.

However, in recent years—with the increase of third-party financing mechanisms, computerized data banks and the immense amount of detailed information requested by government, insurance companies and employers—confidentiality of patient-physician communications and patient medical records has been endangered.

CMA's Position

The California Medical Association strongly opposes the "unethical requirements by third parties that highly confidential medical information be submitted without the patient's fully-informed consent." CMA's Committee on Insurance and Prepayment has been instructed to meet with representatives of the insurance industry to explore means to correct this problem.[1] Similar action has been taken to establish methods of specifically safeguarding the confidentiality of patient hospital records.[2] And, at CMA's request, legislation recently was introduced in the State Legislature—as SB 447—to guarantee confidentiality of patients' medical records in a wide variety of circumstances.[3]

CMA also has sought action from the insurance industry to minimize the amount of patient medical information necessary for insurance reports, and to establish channels of handling this information within an insurance company so that only the medical department of that company has access to it.[4]

Because confidential medical reports sometimes have been made known both directly and indirectly to employers—to the possible detriment of patients—CMA also sought action to prohibit the use of medical information for any purpose other than the evaluation of the specific insurance claim in question, and to withdraw approval of the all-inclusive blanket consent form that patients sign when they apply for insurance benefits.[5]

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WHERE WE STAND

Cost of Health Care*

ESCALATING COST is the most criticized and least understood aspect of health care in America today. In this regard, we cannot emphasize too strongly that health care and medical care are not the same thing.

Medical care—services provided by physicians—is only one part of health care, along with such other components as hospitalization, nursing, dental care, drugs, nursing home care, eyeglasses, etc. Physicians' services account for about 20 percent of all health care costs, while hospital costs account for nearly 40 percent. The rate of increase for physicians' services, furthermore, has been considerably less than the overall rate of increase for health care. In fact, most recent statistics show that the cost of physicians' services—medical care—has been rising at a lower rate than the cost of living.

Why have hospital costs increased so markedly? The primary reason is that hospitals are a service that necessarily involves a high ratio of employees to patients. Labor costs represent about 70 percent of a hospital's total expenses, compared with 25 to 30 percent for other industries. Until recently, nurses and other hospital employees have been notoriously underpaid. As their salaries have risen to more realistic levels, hospitals have had to raise their rates accordingly.

In the future, technical and medical advances will permit even greater feats of life saving than are possible today. But the cost also will be greater, since ever more complex equipment and higher worker-patient ratios will be required.

Physicians certainly are concerned with these rising costs. They keep a close check on them through "utilization review," a process to assure the propriety of doctors' billings to health insurance carriers (see the "Quality Medical Care" section on peer review). Physicians and their medical organizations also seek innovative methods to keep a rein on rising costs; Sacramento's CHAP (certified hospital admission program) and Fresno's Medi-Cal Intermediary Operations are examples of programs that are successfully keeping health care costs down.

But as physicians, our primary concern must continue to be what it always has been—the health of our patients. Therefore, our emphasis must remain on seeing that our patients receive the best possible health and medical care.

Drug Abuse

DRUG ABUSE has become a pressing problem in today's society. Drugs of abuse are defined as "those drugs which produce mood alteration or mind alteration"—those drugs which are psychoactive. The term drug abuse applies to the "use of any drug by an individual to the extent that it adversely affects or limits his ability to function as a responsible person."

CMA's Position

California Medical Association recognizes the extent of the drug abuse problem in our society. CMA has a committee on alcoholism and drug dependence that helps physicians use effective medical countermeasures to the problems of drug abuse and that provides the medical profession with current expert opinion on the subject. The committee also helps educate the public about the dangers of drug abuse.

In 1972, the CMA Council launched a renewed attack on drug abuse in California through a pilot program to increase the ability of physicians to treat drug-dependent patients. The program covers MDs' education and training in diagnosis, treatment and referral to other community health services of patients who abuse drugs, including alcohol.[1] CMA feels strongly that when a person "shows medical indications of physical or psychological dependence on any drug, that person should receive competent medical care." The Association urges the establishment of training programs in medical schools, in community hospitals and at postgraduate levels with extension of training to nurses and paramedical personnel dealing with drug abuse.

In a recent report, the committee listed the drugs of abuse in the order of their physical damage and psychological and socioeconomic disruption. CMA ranks alcohol as the most destructive drug of abuse. Following it, in decreasing order, are barbiturates, amphetamines, heroin and other narcotics, cocaine, hallucinogens, marijuana and hashish, solvents (airplane glue and paint thinner) and tobacco.

"Alcohol abuse is the most serious form of drug abuse in our society today—even more serious than heroin addiction, when evaluated in terms of organ damage, the effect on the user's overall health, societal disruption and association with criminal behavior or total population involved[2]," says CMA. Although CMA does not recommend prohibition of alcoholic beverages, it advocates "intensive public education, in all grade levels and through the mass media, concerning the harmful effects of alcohol," and asks the mass media not to present alcohol in such a way that promotes its use as a mood-altering drug. CMA also strongly believes alcohol must be recognized and treated as a disease that has become a public health concern of major proportions, and that insurance coverage should not exclude the treatment of alcoholism nor place restrictions on the coverage provided, except as those restrictions may apply to any other medical illness.[3]

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*See also Health in the United States.

Because of the increasing abuse of barbiturates and other sedative hypnotics (central nervous system depressants used to treat insomnia and to relieve anxiety) and amphetamines (central nervous system stimulants used to treat certain hyperactive, neurologically-impaired children, to suppress appetite and to ward off fatigue), CMA alerted the county medical societies to the crisis. CMA recommended that "every physician limit the prescription of these dangerous drugs to the minimum quantity consistent with the immediate medical indication[4]."

In its attitude toward addiction to heroin, opiates and other narcotics, CMA asserts that "irrespective of how addiction develops, it is a disease which requires medical services and social rehabilitation. The medical aspects of the disease must be separated from the criminal aspects of the behavior and legal status of the individual patient, so that treatment may be readily available to every addict who seeks it[5]." Because in- and outpatients detoxification clinics, halfway houses and methadone maintenance programs all have been successful to some degree in treating the addict, CMA encourages their availability in sufficient numbers, realizing also that attention must be given to resocialization in an attempt to replace the psychological dependence and establish the individual's personal stability.[6]

Cocaine, used medically as a topical anesthetic, is increasingly used illicitly as a central nervous system stimulant. CMA strongly warns that such continued usage leads to deterioration of health because of nervous fatigue, nutritional deficiency and psychosocial defects and to psychological dependence in the habitual user.

Hallucinogens or psychedelics and marijuana and hashish should undergo intensive scientific investigation to discover their long-range effects, their potential social uses and their value as tools in clinical medical practice.

Marijuana's long-range effects are not known, and CMA encourages research and clinical trials. CMA feels that legalization of marijuana is an issue for society to decide. However, CMA recommends reduction of penalties for possession of marijuana for personal use, because the effects of imprisonment and a felony conviction could create great mental and physical stress. The penalties for the possession of marijuana for personal use, even in private, have imposed criminal status on many persons who otherwise have evidenced no criminal or antisocial behavior.[7]

Inhaling the fumes of solvents can cause mild intoxication, acute disorientation or death. Repeat users may have medically treatable psychosocial problems. The dangers of experimentation with solvent inhalation must be countered by education.

Tobacco is not generally considered a drug of abuse. However, most people are now aware of the direct correlation between cigarette smoking and lung cancer. Even more significant, in numbers of people killed and disabled, are cardiovascular disease, bronchitis and other chronic pulmonary diseases caused by cigarettes. While supporting each person's right to freedom of choice, CMA condemns the use of tobacco as one of the most physically destructive forms of drug abuse in our society today. CMA recognizes the rights of non-smokers to breathe air free from cigarette smoke. CMA encourages individuals to give up the smoking habit, and advocates intensive public education in all grade levels and through the mass media concerning the harmful effects of smoking.[8] CMA's House of Delegates adopted a resolution to discourage smoking in public areas, public transportation, CMA offices and meetings, in all health care facilities; and to endorse a team approach for helping individuals who want to quit smoking. CMA also will develop a placard for physicians' offices saying, in effect, "For your health and the health and comfort of others, we thank you for not smoking[9]."

Drug abuse is not a single, simple issue. It is a collection of many complex, interrelated psychological, physical and social problems not isolated from the other problems of our communities, such as unemployment, housing, education, police relations. Since many aspects of these problems are unique to each locality, local action and involvement are necessary to confront them. California Medical Association recommends the establishment of sound, comprehensive treatment programs for drug abusers in which the whole community actively contributes to social readjustment.

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3. CA 2/9/73; Approved by House of Delegates
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Environmental Health

POLLUTION OF OUR ENVIRONMENT has become an increasingly severe problem of concern for both public and private agencies, as well as individual citizens. The term "environmental health" is used in discussing specific aspects of this problem, such as air, water and soil pollution, but also includes health factors related to population growth, urbanization and technological developments bearing on the quality of life.

The scope of the problem is great. For example, the effects of air pollution on man are serious and can even be fatal; acute episodes of air pollution have caused increased rates of death and disease, especially among the very young and elderly and among persons with preexisting respiratory or cardiac conditions. The immediate threat to human health by waterborne infectious pathogenic agents and toxic materials does not need to be elaborated. Although comprehensive, verifiable data are lacking because specific health costs are difficult to identify and measure, health costs in the United States for environmentally-induced disease have been estimated at an annual rate approaching $40-billion. These costs probably will continue to rise.

CMA's Position

Environmental health is a legitimate concern of the medical profession, and CMA has emphasized repeatedly that overpopulation; pollution of our air, water and land; and other environmental problems have resulted in an "ecological crisis[1]."

Conservation of natural resources is considered an activity and concern of every committee and commission of the California Medical Association and a basic element of CMA's goals.[2] Thus, we have determined to "assume appropriate leadership . . . to achieve recovery and maintenance of an ecologically healthy environment" through (1) educating the medical profession and the public,[3] (2) legislation and (3) encouraging county medical societies to establish environmental pollution control committees[4] and become involved in local ecological activities.[5]

To deal with the serious problem of air pollution, CMA encourages mass transportation, stringent air pollution standards, use and inspection of vehicle emission control devices,[6] mandatory emission inspection and conversion of fleet vehicles to alternate fuels in high-risk areas[7] and use of health warning systems to alert area residents when air pollution levels increase or endanger health.

Noise pollution is another threat to environmental health recognized by CMA. We have urged Congress to allow states more stringent noise pollution standards than federal ones, have supported stringent standards for California, have backed appropriate noise control legislation and supported establishment of noise criteria for California.[8]

CMA urges that the citizens and state government of California endorse the "Environmental Bill of Rights" developed in 1970 by an Assembly select committee,[9] supports the concept of a central state agency for environmental quality,[10] and backed the 1972 California initiative on preservation of coastal lands (Proposition 20).[11]

In regard to the public health dangers of tobacco smoking, CMA discourages smoking in public areas, public transportation and health facilities;[12] and supports a ban on all cigarette advertising.[13]

Some other environmental protection measures supported by CMA: population growth, including family planning clinics; research and action to prevent contamination of our oceans and waterways; adequate sewage and solid waste disposal; use of recyclable and biodegradable products; rat control; maintenance of recreational areas; open-space standards for metropolitan areas,[14] and research funding to assure that nuclear energy development takes environmental factors into consideration.[15]

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5. HDR 25-70
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8. CA 7/28/72
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12. HDR 152-71; HDR 68-73
13. HDR 65-71; HDR 123-73
14. HDR 69-73
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Health Education for the Public

HEALTH EDUCATION is designed to inform and motivate the individual toward practices that will result in optimal health. It goes beyond the systematic transmittal of knowledge that promotes, improves and maintains individual and community health. To be successful, health education also must induce people to apply health information to life and living. The goal of health education is to achieve fundamental changes of life style—away from patterns that contribute to sickness and early death, and toward new patterns that promote good health.

CMA's Position

The California Medical Association has a long history of involvement and commitment in regard to health education for the public. The association currently has a dozen active committees whose primary thrust includes public education as a means of preventing illness and maintaining health. Their names encompass the most pressing health problems of our time, including alcoholism and drug abuse, venereal disease, traffic safety, disaster preparedness and environmental health.

To cite a specific example of work by a CMA committee, our Maternal and Child Care Committee is currently engaged in a program designed to reduce perinatal mortality. Health education plays a major part in this program, stressing the need for prenatal care and personal nutritional education.

An important part of CMA's health education effort is in the area of school health. Our committee on School and College Health sponsored and helped write the "State Framework for Health Education" and the administrative guidelines for its implementation.[1] For more than 15 years this committee also has sponsored many educational programs for professional and lay groups—including school health congresses at CMA's annual session.

CMA's pioneering public education project, "Health Tips," is a further example of CMA activity in this field. These concise statements on specific medical and health subjects, written and approved by panels of medical experts, are distributed on request to more than 6,000 outlets, including nearly 4,000 key school personnel, various news media, public health agencies, physicians and county medical societies. County medical societies and schools—kindergarten through universities—use the material in a variety of ways: duplication and distribution to students and parents in entire school systems, health education course syllabi; health text books, teacher and school nurse education and health fairs. More than 300 subjects have been covered by the four monthly "Health Tips," and many have been translated into Spanish for California's Chicano population.

CMA fills more than 100 monthly requests by schools for films on various health subjects; produces television news films, "Health Hint" public service announcements for radio and news releases for all media; and assists county medical societies with health fairs and exhibits.

CMA also has worked to encourage county medical societies to establish active liaison with local school systems, to provide lectures on appropriate subjects in both the public school system and colleges; and to have physicians and other health professionals make themselves available as consultants and resource people.[2]

Most recently, the CMA Council approved further actions designed to improve public health education. These include: (1) establishing a permanent committee of CMA's Scientific Board on health education for patients and the public, (2) launching an extensive survey of public health educational needs and the adequacy of available resources and (3) exploring methods to encourage physician involvement in health education in the local community.[3]

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"CA" refers to CMA Council action

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2. HDR 96-71
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Health in the United States*

THE PHRASE "health care crisis" is frequently heard in reference to American health care. It appears with some regularity in political speeches and in news media stories.

It is true that improvements in the health-care field are both needed and possible. Undoubtedly, greater efficiency without loss of quality or even with increased quality is possible in some aspects of health care. Better geographical distribution of available medical services—particularly in urban ghettos and rural areas—is needed. And various government health programs need improvement.

However, none of these factors constitutes a "health care crisis." People are not waiting in vain for health care in hospitals, physicians' offices and pharmacies. People are not dying in the streets of our cities for lack of health care. The United States does not have skyrocketing mortality and morbidity rates. These are factors that really would constitute a true crisis—and they do not exist.

Comparing International Health Statistics

Many proponents of the "crisis" theory point to comparisons of selected health statistics for the United States and some western European countries. Our nation's infant mortality rates, they point out, are higher than in some of the smaller European nations, and our statistics for life expectancy are not as good.

But the fact is that comparing such health statistics does not measure the effectiveness or quality of a nation's health care system, nor does it provide an accurate picture of its state of health. For one thing, the relative position of a country in regard to health statistics depends on which statistics are chosen. For example, Sweden is cited for its low rate of infant mortality (also see "root causes of poor health" below). But Sweden also leads most other nations in the world in its rates of death from such causes as pneumonia and stomach ulcers.

In regard to infant mortality statistics, the countries usually compared with the United States have small and relatively homogeneous populations, while the U.S. is a melting pot of various races, cultures and educational and economic attainments—all of which affect health.

Furthermore, the various nations of the world use different bases for reporting their health statistics. In the United States, we count a birth as live if there is any immediate sign of life, while some countries require survival for a year for the birth to be considered live. If we consider areas of the world truly comparable to the United States—Western Europe as a whole or the Soviet Union—our infant mortality rate emerges as superior.

Root Causes of Poor Health

Environmental and socioeconomic factors have a greater impact on a nation's health than medicine alone does. Such causes of death as lung cancer, cirrhosis of the liver, homicide, suicide and automobile accidents are significant factors in this nation's mortality rates. Lung cancer deaths could be cut drastically by a sharp reduction in cigarette smoking. Cirrhosis of the liver could be reduced by a lowered consumption of alcohol. Automobile accidents and death would decrease rapidly with better safety devices and stricter highway law enforcement. None of these problems of society can be solved medically.

Similarly, most studies of high infant mortality indicate that the causes are rooted in poverty, malnutrition and lack of education. Infant mortality, in fact, correlates best with the level of education achieved by the mother. The relatively spectacular drop in rates of infant mortality in this country in the recent past can be attributed in large part to the improvement in income and education from which many poor Americans have benefited since the mid-1960s.

In short, a major portion of America's health problems stem from such non-medical causes as poor housing, poor nutrition, inadequate income and education—and unhealthy lifestyles. Doctors can only treat the symptoms; the medical profession cannot eliminate the root causes of these health problems. This calls for a massive effort on the part of our entire society, involving individuals as well as local, state and federal governments.

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*See also Cost of Care.

How Good Is American Medical Care?

Since comparing international health statistics is misleading, what is a good way to measure how effectively a health care system meets the needs of the people? We believe that the yardsticks by which good medical care can be measured most meaningfully are general health, growth and development; improved life expectancy; eradication of infectious disease and such contagious diseases as poliomyelitis, tuberculosis, typhoid fever and tetanus; advances in medical and surgical techniques for the early detection, treatment and cure of heart disease, stomach ulcers, cancer and other killer diseases. By all of these standards, medical care in this country excels.

Health Quackery

Health quackery has been variously defined, but generally is understood to be "the pretension of practice of a boastful pretender to skill which he does not possess, especially medical skill." The entire spectrum of people needing health care may be involved—from the terminal cancer patient, to the person looking for a quick and easy way to lose excess pounds, and even to the food faddist. Some forms of health quackery cause direct damage to health. Many other forms of health quackery endanger the person's health by delaying proper, scientific medical care.

CMA's Position

From its inception, the CMA has combatted health quackery as a part of CMA's constitutional mission "to protect the public health . . . "

In recent years, CMA sponsored the pioneering 1959 law to protect the public from cancer quackery and in 1967 backed legislation that made California the first state to treat medical quackery as a felony.

Despite this effective legislation, health quackery persists. Cancer quackery, for example, continues to result in tragedy because of delayed or improper treatment of cancer. The medical profession strongly condemns such cancer quackery as the Hoxsey method, Laetrile, the Bolen test, Koch agents, Lincoln Staphage Lysate, Mucorhicin, the Anthrone test and Krebiozen.

The California Medical Association and its component (county) medical societies continually seek to educate the public on the dangers of health quackery and to provide leadership in combatting this hazard.

Health Maintenance Organizations and Prepaid Health Plans

A health maintenance organization (HMO) or prepaid health plan (PHP) can be broadly defined as an organization that contracts to furnish a wide range of health services, both professional and institutional, for a specified population, and is paid a fixed monthly or annual sum per person covered for such services.

Services may be provided either by the organization itself or by arrangements between it and other providers. Basic services that must be provided are not fully determined, but must include physicians' services, inpatient hospital care, and some outpatient services. Under various definitions, it may also include extended care facility services, home health services, emergency care and preventive services. Existing prototypes are the Kaiser Foundation health programs and certain union and railroad health programs.

Plans may be sponsored by a wide variety of agencies, including hospitals, medical care foundations, medical schools, industry and insurance companies. While the total care is to be paid for on a capitation basis, individual providers need not necessarily be paid on this basis. HMO/PHP proponents believe that the fixed operating budget for all health care will encourage the use of the most economical adequate source of care.

CMA's Position

The California Medical Association supports a pluralistic approach to the delivery of medical services, and continues to encourage innovation in the organization and delivery of health care services.[1] CMA considers HMO one such approach; for certain population groups or residents of certain areas, they may provide an alternative means of obtaining health care. However, their development must not be allowed to destroy traditional forms of private medical practice. Patients must continue to have a right to choose the method of receiving care they prefer.

Before any long-term commitment is made to the HMO concept by government, at either the state or the federal level, HMOs must be carefully evaluated in actual operation on a pilot basis. These studies should produce statistical evaluation of cost-effectiveness and critical review of the quality of care provided by existing HMO organizations encompassing at least a two- or three-year period.[2] Pending these results, CMA urges a moratorium on further federal HMO funding[3] and requests the California Legislature to prohibit further HMO contract awards by the Department of Health Care Services.[4] To assist the Legislature in evaluating HMO contract programs—both in terms of quality of care and cost effectiveness—CMA will make available whatever may be required in terms of peer and utilization review expertise.[5]

In regard to HMO contracts awarded by the state, CMA notes that future emergency funding or higher capitation rates may be found necessary to maintain the viability of HMO programs. To provide such assistance and subsidy to this single health care delivery approach and not to others would constitute preferential treatment for HMO contractees and is opposed by CMA.[6]

CMA also points to certain areas in which the Legislature and Congress should regulate HMOs. These include: (1) Approval of need for an HMO by the county medical society or the local comprehensive health planning association; (2) Requirement of substantial physician representation on an HMO's governing body; (3) Requirement that HMOs be regulated as insurers of health care services; (4) Control of HMO's advertising—i.e., treat them as other practitioners of medicine; and (5) Government subsidization only in direct relationship to the number of non-paying patients cared for.[7]

The CMA, working through three of its commissions and committees (Medical Services, Medi-Cal, Peer Review) and in conjunction with four prepaid group practice plans and representatives of several foundations for medical care, developed a list of 24 criteria to be applied in the evaluation of prepaid health plans under Medi-Cal. It is the purpose of these performance criteria to assure that organizations contracting to provide medical services to Medi-Cal recipients can and will provide and maintain the quality of such services.[8]

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"CA" refers to CMA Council action

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Health Manpower

THE SUBJECT of health manpower has received public attention in recent years because of theories that the United States suffers from a "health manpower shortage," particularly a "doctor shortage."

Whether there is an absolute shortage of physicians, or whether problems are essentially ones of distribution, specialization and inefficient utilization, however, remains a moot question—as does the question of what, indeed, represents an adequate physician supply. The topic was confronted in 1972 by the California Medical Association's House of Delegates, which adopted a resolution entitled "Physician Shortage—Myth or Reality[1]."

According to the President's manpower report to Congress last year, by 1980 there will be about 444,000 physicians in this country—enough to eliminate shortages, if in fact they exist. This figure represents a predicted 10-year increase of 120,000 physicians under present educational approaches, as a result of predicted expansions of medical school enrollment and accelerated training. It should also be noted that America's physician population is increasing at a rate three times that of the general population.

CMA's Position

California Medical Association's Division of Socioeconomics and Research recently completed a three-part study—at the direction of the CMA Council[2]—centering on physician supply in California.[3] This study notes that one physician per 650 to 750 persons probably represents a satisfactory, although not necessarily an optimal, level. It further states: "In California, the current figure is one physician per 609 persons. While this cannot be used as absolute, irrefutable evidence that overall statewide shortage does not exist, it strongly suggests that this is the case."

On the national level, the findings of CMA's study seem to agree with the President's manpower report mentioned above: "Nationally, there remains some degree of absolute shortage of physicians with a ratio of one per 779 persons. At the current rate of production of physicians, compared with population growth rates, the gap should be closed within the next few years."

Nonetheless, it is a fact that people living in the poorer sections of many cities and those living in rural areas isolated from cities and towns often do not have ready access to a doctor. Clearly, then, a major health manpower problem is maldistribution of physicians.

CMA is working toward alleviation of this problem in California through our Physician Placement Service, created specifically to "match" physicians with locations where opportunities exist and where medical services are needed.

In order to assist areas that have a physician shortage, CMA also supports legislation to grant income-tax credits to medical practices established in such communities and areas.[4] In other activities, a CMA consultation service is being created through our Commission on Health Manpower to help identify and solve problems relating to the accessibility of care in both urban and rural areas. This service will stimulate county societies to identify gaps in their areas' health care delivery systems and will help them develop realistic solutions to these shortcomings.

Through the California Medical Education and Research Foundation (CMERF), a nonprofit corporation supported by CMA, the association is able to provide financial assistance for innovative local medical care programs in their early phases of development. In addition, CMERF often is called upon to help county medical societies develop grant applications for funds from private and public sources. Recent examples of such grant applications include financing programs of health insurance for migratory workers and evaluating the effectiveness of neighborhood health centers.

Furthermore, CMA is giving college scholarships to many deserving students, particularly blacks, who plan careers in the health field. And we are urging medical schools to expand their enrollments and to seek out and financially assist interested and potentially qualified minority students who desire educations in the health fields.[5]

To further alleviate the health manpower problem, the association is working toward establishing the new occupation of "health care assistant," also known as "physician's assistant." In cooperation with other interested organizations, CMA has developed criteria for the education of this new category of health worker, worked on legislation for their certification and studied means for recruitment and employment.[6] To assure that education and utilization of health care assistants serves the best interest of quality patient care, CMA emphasizes that all new health assistant categories and programs should be reviewed by CMA's Commission on Health and Scientific Board.[7]

CMA's commitment to an adequate supply of health manpower to meet California's future needs is underscored by our active campaign on behalf of Proposition One in 1970, which failed, and Proposition Two on the November, 1972, ballot, which voters approved. CMA contributed staff and financial assistance toward the passage of these bond issues to upgrade and expand the state's medical schools and other health manpower training facilities.

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National Health Insurance

THE TERM "national health insurance" has been applied to a wide range of proposals dealing with the financing and delivery of health care in this country. Since these proposals differ greatly among themselves, the term "national health insurance" (NHI) cannot be strictly defined. However, common to all of these proposals is the use of some form of insurance, private or social, to pool the financial risk of needed health services and the use of some form of federal taxation to assist in paying for the services or for the insurance.

In general terms, the major current proposals can be classified either as private insurance approaches, such as the American Medical Association's Medicredit plan, or social insurance proposals, such as the Kennedy-Griffiths-AFL/CIO bill. As would be expected from their use of the private insurance approach, the former proposals involve less compulsion and more choice than the social insurance proposals. The social insurance plans would mandate inclusion of the entire population; the private insurance proposals could include everyone, but individuals might choose not to participate.

AMA's Medicredit would cover the lower-income group in full, with income-tax incentives to all other persons to encourage the purchase of comprehensive basic health insurance coverage. Insurance premiums for protection against catastrophic health expenses would be paid in full, without regard to income level.

The social insurance plans would pay for virtually all services, while the private insurance plans would set minimum basic benefits and allow a purchaser to select these or greater benefits at his option.

Administration and financing of the proposals varies widely. The estimated costs differ accordingly, from about $40 billion to more than $80 billion for the social insurance programs, to low and high cost estimates of $8 billion to $17 billion for Medicredit.

Both types of proposals would provide financial access to the health care system, but from opposite positions as to the rights and responsibilities of the individual and government. The social insurance proposals would give almost total financial control of the health care system to the federal government and subordinate the rights and responsibilities of both patients and health care providers. The private insurance programs would provide the individual with financial access to the system and make governmental intervention subordinate to the individual's decision.

CMA's Position

CMA believes that physicians must assume the responsibility for making sure their patients get the kind of medical and health care they need and want. Patients must not be forced into an assembly-line health care system that does not recognize that medical care, in the final analysis, is one sick patient treated by one physician he trusts. Consequently, CMA repeatedly has voiced strong opposition to any policy of *compulsory* national health insurance.[1]

Recognizing the individual as the important focus in the health care system, CMA in recent years has developed a number of principles deemed essential to any program of national health insurance.

First is adequate coverage for all. Everyone should be able to get the health care he needs; no one should lack health care simply because he cannot afford it.[2]

Second is complete freedom of choice.[3] Freedom to join or not join the plan.[4] Freedom to choose one's own doctor and health facility.[5] And freedom for the doctor to give sound medical treatment without bureaucratic interference.[6] In addition, confidential physician-patient relationships must remain inviolate and without third party interference.[7]

Third is comprehensive health care. In addition to adequate standards for hospital and medical care, any plan should cover outpatient services, prescriptions, dentistry and nursing care. Catastrophic illnesses must be covered to avoid financial ruin for patients.[8]

Fourth is sensible financing. Financing medical care through the voluntary, private insurance approach is the means whereby individual freedom and responsibility can best be assured, but prepaid closed-panel plans should be available as an option.[9] Government assistance should be provided to those unable to pay for medical care.[10] For others, government might pay part or none of the costs, depending on income.[11] "Usual, customary or reasonable" fees should be paid providers of health care.[12] There should be no duplication of health care coverage. Just as personal health care insurance plans cannot provide duplicate benefits to subscribers, so no government-sponsored program should duplicate that provided through employment. Multiple coverage for the same individual is inappropriate.[13]

Fifth is innovative care. No NHI plan should be locked into any one health care system. New ways to deliver care should be encouraged within a pluralistic system, so doctors can meet the medical needs of the future.[14]

A sixth point concerns pilot projects. We have seen what upheaval can be caused by government health care programs implemented nationwide without prior testing to determine their effect both on the health of patients and on the soundness of the health care system. Therefore, we believe that experimental programs such as health maintenance organizations (HMO's) and others should be tried on a pilot basis.[15] Demonstration and experimental programs should involve both local medical societies and consumers.[16]

Seventh is professional standards. Medical professionals must establish standards for the care received by the patient[17] and must monitor that care to evaluate both quality and appropriateness of charges.[18] Professional medical organizations have the training and experience to do this; government does not.[19] In addition, CMA believes that the same mechanism and standard of peer review must apply for all methods of medical care delivery; the peer review committee must be under the control of the local medical society, and its decision must be binding.[20] Further to assure quality care, institutions should be accredited and utilization review committees maintained.[21]

Eighth is knowledgeable planning. CMA feels that practicing physicians must be represented effectively in decision-making on all governing boards and at all administrative levels involving medical care delivery.[22]

CMA believes these principles are medically sound and socially progressive. They encompass a realistic view of what is fiscally feasible in making health care available, without placing unrealistic burdens on the wage earners and businesses of the nation. Of all the national health insurance proposals currently being considered, AMA's Medicredit plan comes closest to complying with CMA principles. Consequently, CMA officially endorses Medicredit.[23]

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"CA" refers to CMA Council action

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Physician's Assistants

In some areas of America it sometimes can be difficult to obtain health care services. One reason is a shortage of physicians, particularly family physicians, in some rural and inner city areas.

To help overcome this problem, a new type of health worker, the physician's assistant, is being developed. In the health manpower pyramid, the physician's assistant is below the physician and above the registered nurse. Creation of this new type of health worker assumes that many of the physician's more routine duties can be effectively assumed by a lesser trained health worker, freeing the physician to treat the more complex medical problems of a larger segment of the population. Physicians utilizing physician's assistants also are freed to master new skills made possible by new developments and expanded knowledge and technology in medicine.

Several educational programs for the physician's assistant have been developed and others are currently being formed in California, each required by AB 2109 of 1970 to have the approval of California's Board of Medical Examiners.

As a graduate of the approved program, the physician's assistant, under the responsibility and supervision of the physician, should be able to perform such duties as taking a "complete, detailed and accurate history; performing a complete physical examination excluding pelvic and endoscopic examination; and recording and presenting pertinent data in a meaningful manner to the physician. He should be able to perform and/or assist in the performance of routine laboratory and screening techniques such as blood tests, urinalysis, taking of cultures, performance and reading of skin tests, and the taking of electrocardiograph tracings, in addition to being able to give injections, immunizations, removal of sutures and casts, application of traction, removal of foreign bodies from the skin, incision and drainage of superficial skin infections, and strapping, casting and splinting of sprains. He should be able to recognize and evaluate situations calling for immediate attention of the physician, instruct and counsel patients in certain matters, assist in hospital admissions and in the physician's office in the ordering of drugs and supplies, record keeping, and the upkeep of equipment, assist the physician in providing services to patients requiring continuing care, and facilitate the physician's referral of patients to appropriate health facilities, as well as have an understanding of the socioeconomics of medicine, the roles of various health personnel and of the ethics and laws under which medicine is practiced and governed."

CMA's Position

Recognizing the shortage of physician manpower in California, the California Medical Association sees the role of the physician's assistant as one possible solution to the situation. For more than three years CMA has studied the assistant's functions and effects on the quality of health care delivery.[1] "To insure that the role of the physician's assistant is directed toward enabling the physician to work more effectively and not toward developing unqualified and insufficiently trained 'second class' practitioners,[2] CMA's Commission on Allied Health Professions has been charged with the task of assisting the Board of Medical Examiners in developing criteria for the physician's assistant[3]."

CMA urges that the physician's assistant remain under the direction of a physician, "be certified with some mechanism of recertification including peer and specialty review," and be so identified to patients.[4]

CMA strongly affirms that the physician's assistant shall neither restrict a physician's medical practice management and judgment nor shall he abridge the physician's authority to use and direct allied health personnel in accordance with sound medical practice.[5]

Concerned with establishing and maintaining high criteria for medical training and educational programs for the physician's assistant, the House of Delegates directed CMA's Commission on Health Manpower and Scientific Board to review and consider for approval all new health assistant categories and programs in California before their implementation by any educational institutions.[6]

The shortage of health manpower is of grave concern to CMA, and continuing efforts have been directed at relieving this shortage. Because CMA realizes that physician's assistants are only one answer to the problem of health manpower shortage, CMA continues to seek additional solutions—the prime purpose being improvement in the quality of health care services.[7]

REFERENCES

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Physician Unions

"PHYSICIAN UNION" is a general term covering a variety of organizations that seek to apply union techniques in representing physicians. Recently, a number of these groups have sought to include dentists as well. Some physician unions have chosen to affiliate with organized labor but most have avoided this step.

Arising at a time when government and insurance plans exert growing influence, the physician union movement is concerned primarily with members' economic interests and their frustration with "third party" intrusion into the doctor-patient relationship. Many physician-union leaders feel that such traditional organizations as the American Medical Association and the American Dental Association are doing excellent work in the fields of professional standards, postgraduate education and medical and dental ethics. However, they state that there has been too little militancy in socio-economic matters.

CMA's Position

The California Medical Association recognizes the right of its members to join physician unions and desires to maintain continued communication with these organizations.[1] However, in regard to using organized labor's tools of striking, boycotting or withholding services, the CMA House of Delegates has emphasized repeatedly that such actions are unacceptable and unethical for the medical profession.[2]

More generally, CMA has noted that existing antitrust laws would seem to prohibit organizations of self-employed persons from engaging in collective bargaining. Since most practicing physicians today are self-employed, this factor would appear to limit physician unions legally to the same activities presently undertaken by organized medicine.[3]

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Professional Standards Review Organizations

WHERE WE STAND

THE SOCIAL SECURITY AMENDMENTS passed by Congress in 1972 included the Bennett Amendment that established professional standards review organizations (PSROs). These peer review mechanisms are designed to "promote the effective, efficient and economical delivery of health care services . . . and to assure, through the application of suitable procedures of professional standards review, that the services for which payment may be made (for Medicare, Medicaid and Maternal and Child Health Programs) will conform to appropriate professional standards for the provision of health care."

The Secretary of Health, Education and Welfare is empowered to contract with "qualified organizations" to establish PSROs for a trial period of up to two years. After January 1, 1976, the secretary may contract with other organizations, if he finds that local professional groups were unable or unwilling to perform the review function.

To be designated a PSRO, an organization must be deemed by HEW to be "qualified"—a nonprofit, professional association with a voluntary membership of licensed doctors of medicine or osteopathy (usually 300 or more) who are practicing medicine in the area and who are not required to pay dues to any organized medical society as a condition of PSRO membership.

The PSRO must determine whether services are medically necessary, quality meets professionally recognized standards and the location where services were given is appropriate. PSROs will have authority for advance determination over elective admissions to hospitals and long-term-care facilities and over extended and costly treatments. The responsibilities initially may apply only to institutional care, but ultimately will apply to all health care under Medicare, Medi-Cal and Maternal and Child Health programs. A statewide professional standards review council will coordinate activities of all PSROs in the state and will help evaluate their performance.

CMA's Position

When Congress was considering the Bennett Amendment to the Social Security laws, the California Medical Association strongly opposed its PSRO provisions, stressing "the tremendous amount of ongoing, organized effort by the medical profession in the area peer review and its conviction that no nationwide 'blanket' approach in this area would fit our needs in California[1]." It urged Congress to "allow states of proven capabilities in the area of peer review to continue to advance their quality and cost-monitoring systems, in concert with fiscal intermediaries and county societies[2]." Furthermore, CMA stressed the dangers to quality of care inherent in mechanisms concerned primarily with cost control.

When PSROs became law, the CMA Council voted to "continue to be a strong advocate in defense of the (medical) profession whenever regulations or administrative policy interferes with the practice of medicine[3]." CMA will continue to "support, encourage and strengthen its Peer Review Commission and all functions related to quality assurance, including: medical staff survey activity; development and publication of medical policy information; appeals committee activity; and continuing education programs."

The California Medical Association, "when requested, will offer full assistance to any society or its foundation which expresses an intent to establish a PSRO, but will not actively encourage those societies which do not seek to establish a PSRO to develop one. Instead, CMA will urge those societies to support and strengthen peer review as a medical society/association function. CMA will continue to support local jurisdiction over professional review and quality evaluation, and will offer advice and consultation to government in its development of regulations of the Bennett Amendment."

CMA House of Delegates agreed that "an effort should be made to establish a role for the Peer Review Commission which parallels that of the Statewide Professional Standards Review Council, while striving to become the primary coordinating resource to the Council[4]." CMA has launched an educational and information program regarding CMA's Peer Review Commission, the Bennett Amendment and PSROs to its membership and component societies, emphasizing person-to-person communications by physician leaders.

In addition, CMA is working with county medical societies to identify rational medical service area boundaries and a masterplan is being prepared to present these PSRO area preferences to the federal PSRO office.

Because medical care needs in California are both varied and complex, peer review continues to be a dominant theme with CMA. It is a dynamic, evolving process which the medical profession recognizes as its responsibility. This responsibility extends to all services provided by or ordered by physicians, and is equally applicable to various delivery systems ranging from solo practice to highly-structured, closed-panel approaches. CMA believes, however, that quality, not cost, must always be the paramount concern of physicians, in the best interests of their patients. (see "Quality Medical Care")

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Quality Medical Care

Peer Review, Continuing Medical Education

MAINTAINING AND IMPROVING the quality of medical care have long been areas of intense concern for the medical profession. With increased demand for services and increased involvement by government and other third parties in the medical care field, the profession's quality assurance programs are essential activities in the public's behalf.

California physicians have developed an effective and nationally recognized system of "peer review" (described below). Peer review is defined as the evaluation by practicing physicians of the quality and efficiency of services ordered or performed by other practicing physicians. As generally used, peer review is the all-inclusive term for professional medical review efforts, ranging from credentials review to disciplinary action when necessary.

Continuing medical education for the physician is another aspect of the profession's effort to assure high quality medical care. Here again, California physicians have developed a program considered a model for the nation (outlined below). Continuing medical education is defined as educational activities designed to reinforce the physician's basic medical knowledge and inform him of new developments within his field through refresher courses and supplemental study. The importance of this activity is underscored by the rapid progress of medical science—a doubling of medical knowledge approximately every seven years.

CMA's Position

PEER REVIEW

California Medical Association is firmly committed to the concept of peer review, because only practicing physicians are equipped by education, training and professional experience to evaluate the medical care provided by other practicing physicians.[1] Consequently, CMA sees peer review as the appropriate and essential function of state and county medical associations, hospital staffs and other physician sponsored organizations.[2]

How does a peer review work?

On the local level, qualifications or credentials committees maintained by county medical societies and hospital staffs investigate the credentials of all applicants for membership, make recommendations regarding membership and staff privileges, review records to arrive at a decision regarding performance and competence, and investigate any breach of ethics that may be reported. Patterns of practice and professional conduct questions are reviewed by the peer review and mediation committees of county medical societies. Foundations for medical care—and their work in local health insurance claims review—are an extension of that activity.

Within the hospital, doctors' diagnosis and treatment are reviewed by a variety of committees established by doctors. Tissue committees review the indications for surgery from reports on tissue taken during surgical procedures—and report evidence of unnecessary or questionable surgery. Utilization committees monitor the necessity and length of hospitalization. Medical procedures committees analyze medical procedures, including the medical management of surgical patients.

In 1971, a special commission was established by CMA[3] to expand, coordinate and refine physician peer review activities concerned with quality of medical care and utilization. CMA's Peer Review Commission assists local peer review groups, provides a central clearinghouse for peer review information, develops comparative data, administers appeals and assures public accountability. Most recently, CMA also established a Public

Advisory Council to provide information on the public's views concerning problems of health care quality and costs.

Our Medical Staff Survey Program is another CMA approach to assuring quality medical care. Since 1959, this voluntary program has been making thorough on-site reviews of hospital medical staff performance. Now also conducting surveys jointly with the Joint Commission on Accreditation of Hospitals (Consolidated Hospital Surveys), the program draws from a panel of 180 practicing physicians, as well as utilizing hospital administrators from the JCAH. Hospitals meeting the stringent survey standards are awarded seals of approval. A similar program of staff review for long-term care facilities was initiated recently by CMA.

CONTINUING MEDICAL EDUCATION

The field of continuing medical education provides another example of CMA activities designed to assure high quality care to patients. Since 1934, CMA—in cooperation with the State's medical schools—has sponsored its own postgraduate education programs to keep physicians up to date. These and other programs now represent nearly 50,000 hours of instruction yearly in California. For many years, CMA also has served as a statewide center for coordinating and publishing of postgraduate medical education sponsored by a variety of participating organizations—hospitals, medical schools and so forth.

Recognizing that continuing medical education has become increasingly necessary "to enable the physician to render the best possible care for his patients in this day of rapidly expanding medical knowledge[4]," CMA officially launched a unique new program in 1970. It consists of "certification" for California physicians—regardless of CMA membership—who voluntarily participate in a minimum of 200 hours of approved postgraduate educational activities in a three-year period; already more than 10,000 doctors are voluntarily participating in the certification program.

A related program is CMA's "accreditation" of the continuing medical education activities of health facilities—the first state-level program of its type in the nation, and one which 31 other state medical associations have used as a model. The emphasis of this voluntary accreditation program is on improving the quality of continuing medical education, on making it responsive to the needs of practicing physicians and on making it effective as a means of improving patient care. Audit workshops in continuing medical education are held to assist hospitals in defining their educational needs and dealing with them effectively. Another important aspect of the accreditation process is an ongoing program of evaluation to determine that educational activities actually have been effective in improving patient care.

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2. HDR 73-71
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Refer to: Shapiro MJ: Blue Shield, the doctor and the public they serve. Calif Med 119:60-65, Dec 1973

Blue Shield, the Doctor and the Public They Serve

MARVIN J. SHAPIRO, MD, *Encino*

One of the most important issues soon to be debated, discussed and acted upon by our political leaders—with the inevitable legislation—will be the methods by which the people of this country pay for and accept the delivery of health care services.

Volume upon volume of testimony from hearings of congressional and senatorial committees dealing with the financing and delivery of health care services has been heard and recorded.

Concomitantly, a mountain of legislation initiated by members of Congress of widely divergent opinion stands ready to be acted upon.

Politically speaking, the issue of health care is upon us.

A Look at the Past

It is interesting to note that the social and economic pressures and the resultant political responses now facing organized medicine and health care are remarkably similar to those of the 1920's and 30's. It was in this kind of climate and in response to similar challenges that Blue Shield of California (then known as California Physicians' Service, the plan's official corporate name) was founded. The date was February 2, 1939.

Back in the late 1920's, a national commission (The Committee on the Cost of Medical Care) was formed to study the cost of medical care. Heading the commission was President Herbert Hoover's Secretary of the Interior, Doctor Ray Lyman Wilbur. Within a few years Doctor Wilbur, one-time president of the American Medical Association, would become the first president of California Physicians' Service.

Actually the stage was set by Doctor Wilbur in a speech before the American Academy of Medicine in 1913. He made it clear to his audience that doctors had a social as well as a medical responsibility to their patients. As dramatic advances in medical science and technology became translated into services to the patient, medical treatment became increasingly expensive. Doctors required longer and more expensive training periods. Hospitals, laboratories and offices required more complex and expensive equipment and more highly trained technical personnel to operate that equipment. These increased costs had to be reflected in higher hospital charges and physicians' fees. Some method was needed by which the average budget could be made to meet these increasing expenses—a method which would provide insurance to protect the average family for the ever increasing costs of illness.

The debate reached the California Medical As-

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sociation House of Delegates in 1935 when proponents of a compulsory health insurance plan succeeded in obtaining the House of Delegates' endorsement of a concept of compulsory health insurance which would be financed through taxation. However, the following year, after heated debate, that position was reversed. Instead, the California Medical Association endorsed and committed itself to another new and yet unproven concept—organized medicine could and would support and sponsor a statewide health care prepayment plan.

With the players in position and the issues clearly drawn, the gauntlet was thrown in the form of Culbert Olson's election as Governor of California. A liberal reformer, Olson was elected on a platform which strongly urged the establishment of a compulsory health insurance program paid for through state payroll taxes.

In response to the electorally expressed will of the people (and already on record as supporting the theory of a voluntary statewide health care prepayment plan) the California Medical Association preempted Governor Olson's government-sponsored involvement in health care with the incorporation of California Physician's Service as the first statewide nonprofit prepaid health care financing organization in the nation.

Blue Shield was organized to provide, on a contract basis, the cost of physician services based on the principle of freedom of choice of provider and fee-for-service through a prepaid membership arrangement.

After operating in a condition of legal limbo for several years, California Physicians' Service and the CMA urged the State Legislature to adopt appropriate enabling legislation. In 1941, a bill was passed stating that a nonprofit corporation could be organized for the purpose of providing physician services and other professional services. This non-insurance status was upheld in 1946 by a decision of the California State Supreme Court which stated in part:

> Probably there is no more impelling need than that of adequate medical care on a voluntary, low-cost basis. The medical profession, unitedly, is endeavoring to meet that need. Unquestionably, this is a service of high order . . .

During the corporation's infancy, Physician Members—committed to the concept of assuring Blue Shield subscribers (their patients) a predictability of the cost of sickness—found themselves in the position of accepting less than their billed amount in order to help the organization through its financially perilous early days. This dramatic display of support for the service benefit concept promulgated by Blue Shield proved to be a great service to the patient, the community in which the Member Physician practiced and to the medical profession. As a result, Blue Shield gained public acceptance and became the important source of health care financing it is today. Unfortunately, several fly-by-night operations also sprang up throughout the state. Sometimes they copied Blue Shield contract forms word for word and attempted to peddle "prepaid health care protection" which was oftentimes worthless.

It was obvious that more definitive legal action was needed and it came in the form of legislation—the Knox-Mills Health Plan Act—which was adopted at the urging of CMA and Blue Shield. As a result of the Act, any health plan in California which is not an insurance company (and therefore not regulated by the Insurance Commissioner) must register with the Attorney General's office and be regulated by that office.

Throughout the years, Blue Shield's guiding principle both philosophically and as a business organization has been predictability of cost to the subscriber. The willingness of Physician Members to voluntarily accept Blue Shield's payment as payment in full for covered services is the foundation upon which that predictability is built. Because of his commitment to providing medical care on a fee-for-service basis combined with the right of the patient to choose his own physician, the Blue Shield Physician Member accepts this contractual responsibility.

Physicians must be willing to do their share to assure the financial stability of a voluntary health care system. Today, more than 18,000 California physicians demonstrate their role as responsible citizens in their community and within their profession by supporting the principle of providing quality health care protection at a reasonable and predictable cost as Physician Members of Blue Shield. To paraphrase an exhortation familiar to all of us, the physician must ask not what Blue Shield can do for him as a doctor, but what he can do for his patients by being a Physician Member of Blue Shield!

Why Does a Physician Join Blue Shield?

The leadership and direction for Blue Shield's medical and financial policies come directly from physicians who are elected to the Plan's Board of

Trustees by the CMA's House of Delegates. In addition, administrative laymembers of the Board representing the subscriber's concerns are also selected and appointed by the House of Delegates.

Physician support and guidance is essential if Blue Shield is to remain in operation as it is now structured and, also, if it is to continue to render what the State Supreme Court termed "service of a high order." A physician's decision to join Blue Shield has undoubtedly been based on many factors, not the least of which is the guarantee that he will be paid directly for his services. Initially, "paid-in-full" type payments to Physician Members were made on a fee schedule basis. That "paid-in-full" service benefit feature, however, applied only in cases where the subscriber's annual income fell below a certain level, which at one time was only $2,500. As more and more subscriber incomes rose above the ceiling income level, Physician Members billed the subscriber for additional amounts over and above the fee schedule. Furthermore, the fee schedule was becoming less representative of the principles which led to the founding of Blue Shield. Therefore, a more equitable payment mechanism for both physician and subscriber was needed. What ultimately emerged was an innovative and uniformly applicable system, known today as the Usual, Customary or Reasonable fee concept.

Nearly 90 percent of Blue Shield business today provides for Usual, Customary or Reasonable payments for physician charges. In addition, with the increasing number of Blue Shield subscribers, Physician Members today are receiving more and more payment for their services directly from Blue Shield.

An important role inherent in Blue Shield's operations is the effort that goes into maintaining and developing a continuing dialogue of two-way communications with physicians and their medical society representatives through various methods of instructions, guidance and consultations, conducted by the Professional Relations Division. These activities result in as many as 10,000 field calls a year to physician offices to assist the doctors' office staffs with methods of proper claims submission and to resolve special inquiries and problems which may arise between Blue Shield and the individual physician. No other health payment organization goes to such lengths to assure a better working relationship with the physician.

It should be added at this point that the commitment to freedom of choice of provider and the private practice of medicine is a dual responsibility. In addition to the Physician Members' dedication to the service benefits concept, the individual subscriber also plays an important role in preserving fee-for-service payments for health care. For, if he is to be assured predictability of cost, the subscriber has an obligation to obtain services from a Physician Member.

What Are a Physician Member's Obligations?

In the interest of preserving the voluntary fee-for-service system, Physician Members assume certain obligations when they join Blue Shield. First, they agree to provide any medically necessary services to subscriber members of the Plan, and to send their bill directly to Blue Shield if that service is a covered benefit of the member's contractual agreement. This is the service benefits concept upon which the Blue Shield Plan was founded. Second, Physician Members must look solely to Blue Shield for payment for covered services provided to subscriber members. In most cases, the level of payment will be based upon Usual, Customary or Reasonable (UCR) charges as determined by Blue Shield. That UCR payment determination involves comparing, by electronic data processing, the millions of individual fee charges with every medical procedure listed in the CMA Relative Value Studies and establishing an individual physician's profile of charges, based on his usual fees for particular medical procedures during a certain time period.

To establish the customary range, the physician's usual fees are compared to the usual fees of his peers in a particular locale, and a customary range of charges is determined. At present, Blue Shield has established the customary profile for a given procedure to be at the 75th percentile of usual charges in a defined geographic area—in other words, the level at which at least 75 percent of the doctors' services in a community would be fully paid. Physician Members, by accepting payment for charges which are reduced to the 75th percentile, even though they may not have been the physician's usual charge, play an increasingly important role in keeping the lid on the rising cost of health care. This is an effort of which all Physician Members can be proud.

If a particular charge exceeds an individual physician's own usual charge for a given procedure, and also exceeds the customary charge established for that procedure, the payment is reviewed by physician consultants who work part-time for Blue Shield. These consultants determine the reasonableness of the charge. If necessary, a committee of the billing physician's own local medical society is called upon to ascertain the validity of the charge.

Experience has proven, however, that in the vast majority of instances, the physician's charge is well within the normal limits and Blue Shield's payment is accepted as full payment.

Blue Shield recently updated physician profiles. Actually, before the September 4 profile system update, about 51 percent of the claims received under UCR programs were paid in full and an additional 36 percent were paid at a level that fell within five dollars of the amount originally charged. Now, with physician's payments based on charges received from January 1 through December 31, 1972—the most current annual charge data available—it is estimated that 85 percent of all Standard Business claims, for covered services, will be paid as billed.

By accepting Blue Shield's determination as payment in full, and not passing the difference on to the patient, we have a built-in guarantee to the subscriber which gives him an absolute predictability of cost for his health care dollar.

Another obligation the physician assumes, though it was only enforced very early in the Plan's history and again quite recently, is that of "helping out" if the organization is in financial difficulty. (As was previously noted, payments accepted by physicians in the early days were in many cases a small fraction of the total billed amount.) Recently, Physician Members were again called upon to help their corporation. During a six-month period in 1971, a 5 percent withholding of payments was imposed. The funds withheld helped Blue Shield stabilize its reserves after a devastating two-year period when medical service utilization reached totally unpredictable heights. On December 31, 1971, the withholding was terminated. A commitment was made that Physician Members would later receive full payment of the amounts temporarily withheld. In October of this year, that promise was kept and the withheld $655,000 was paid.

This kind of physician support vividly demonstrates to the purchasers and users of health care benefits that physicians are willing to do their share to assure the financial stability of a voluntary health care system. Consistent support from physicians and subscribers emphasizes the validity of Blue Shield as an alternative to total government control of health care delivery and financing. However, even with the voluntary system it is still necessary—and desirable—that there be a government-private sector relationship to serve certain segments of our society.

Government Sponsored Programs

Blue Shield's involvement in federal and state programs, enabling the poor, the medically indigent and the elderly to receive medical services, is only natural in light of its historical relationship with government health care programs. Furthermore, it is wholly consistent with the motivation of those California physicians who founded the plan in the late 1930's. In fact, the preamble to the organization's constitution, which was written at that time, states that one of the reasons for organizing California Physicians' Service was to create a vehicle which would permit services to be provided under medical auspices without direct government intervention, in the event government did, at any level, get into the provision of physician services.

Had it not been for Blue Shield's experience and ability in claims processing, government planners might have been successful in their attempts to assume complete control and actually operate all phases of government health care programs. But, because of its relationship with practicing physicians and with Blue Shield subscribers, the Plan was in an ideal position to serve as a buffer between government and medicine, thus helping assure a necessary balance between the government bureaucracies' strong interest in economic controls and physicians' interest in quality of medical care. Today, Blue Shield continues to maintain this buffer role.

At the direction of the California Medical Association House of Delegates, Blue Shield assisted the government in getting Medicare and Medicaid into operation with as much influence from the private sector as possible in the medical and surgical portions of the program. (Without Blue Shield —the only bidder for Medi-Cal—the program would have begun in 1966 completely under government operation.) This has benefited beneficiaries, providers of care and, ultimately, taxpayers who would have borne the cost of re-creating organizational structures capable of handling these massive government programs.

Because of Blue Shield's unique position, every new directive affecting one of the various government programs has been reviewed in advance keeping in mind the legitimate concerns of the medical profession. As a result, frequent modifications to initially proposed procedures and policies have been achieved. Unfortunately, in some instances, Blue Shield has borne the brunt of criticism in cases where the victory has not been complete.

I know of no other organization subjected to as many checks and balances and reviews in the administration of its business. Indeed, we walk a very fine line. Our ability to function independently is limited by the desires of the California Medical Association through the Council Members on our Board of Trustees; by the practice of referring certain subjects to CMA committees; by our network of subcontracts with Foundations for Medical Care; by cooperative arrangements with Blue Cross; by government contract limitations and regulations; by review by the entire CMA House of Delegates; by the steady stream of state and federal auditors; and more.

It is obvious that physicians would be unable to provide the influence and direction affecting the provision of care they now have available through Blue Shield if the future course of health care financing and delivery were to be directed by a government agency or a private commercial insurance company responsible to its stockholders and generally unconcerned with the impact on the practice of medicine their management's decisions might have.

Through this system of accommodating the government through private sector administration, needy recipients are provided with health care they need, medicine maintains a voice in the structure and administration of the government's programs, and quality and cost control are handled by those most able to maintain the necessary balance between payor and provider.

Blue Shield continues to assist the medical profession in demonstrating its ability to be responsive to and responsible for the health care needs of the nation. This history of providing a bridge between government and the medical profession has been an important element in America's health care system.

Now, with increasing clamor for totally federalized health care, the lessons learned and experience gained during more than 33 years of operation can provide the basis for assuring that the public will receive the best health care possible from the most highly trained professionals, at reasonable cost only if administration and control are largely retained in the private sector.

During the first seven months of this year, Blue Shield, through its prepayment and utilization review mechanisms, effected cost containment savings to the public of more than $67 million. This is positive proof to critics of the private sector that Blue Shield and the medical profession play an important role in helping to keep the lid on the cost of health care. We are determined to make positive stories of this nature available to all segments of society so that informed opinions can be formulated in response to certain pie-in-the-sky programs envisioned by some for the future.

The Future Role of Blue Shield

What about Blue Shield's future role? Can it remain an integral part of the nation's health care system? Obviously, the answer must be yes. Although there is surely much that still needs to be done, Blue Shield's future can be assured—especially if it maintains its founding principles of being responsive to the legitimate requirements and concerns of physicians on the one hand while serving the "high public order" on the other.

Financially, Blue Shield's future is quite optimistic. Last year the combination of record-breaking sales and effective cost containment activities combined to increase the organization's stabilization reserve fund by more than $7 million. Remarkably, after only six months in 1973, the Plan surpassed last year's new record high sales by selling more than $17.2 million (annualized) in new group business compared with $14.8 million in annualized dues for all of 1972. In all, more than 1.1 million Californians subscribe to Blue Shield. It is worth mentioning particularly that Blue Shield's retention rate on existing business for the first six months of this year was at a record high of almost 99 percent.

Of special interest to those who closely watch Blue Shield's activities is the highly successful implementation of the new Medi-Cal Intermediary Operation (MIO), a cooperative venture among the two Blue Cross plans and Blue Shield to administer the Medi-Cal Program. This innovative marriage of sophisticated electronic claims processing techniques and improved communications with health care providers has proved to be a model of how the private sector can and should administer large and complex public programs.

Clearly there is a role for Blue Shield to play in the future. The health care dollar is one of our nation's most precious commodities. It must be spent wisely. With Blue Shield and the medical profession working together, this principle of service can be accomplished. The future role of Blue Shield of California is mostly dependent upon its ability to prove that, through its unique relationship with the medical profession, as a doctor-sponsored prepaid health care financing plan, it can provide a fee-for-service system which assures the consumer predictability of cost. The cost for health care services must be as fair as possible consistent with assurance of high quality.

The future will of course bring changes both in the methods of delivering care and the way in which we pay for care. If the medical profession is to influence the direction of national policy, I believe there is no more effective way than through its active participation in Blue Shield as Physician Members. Without doubt, lack of substantial physician support of Blue Shield would be detrimental to the voluntary private practice of medicine.

Fee-for-service with freedom of choice is the system of practicing medicine preferred by most physicians, and it is clearly in the best interest of the public. However, it is obvious today that there is a strong push from both Republicans and Democrats in Sacramento and Washington for alternative delivery systems. The field is littered with a multitude of programs designed to finance and deliver health care services—PHPs, HMOs, capitation, cradle-to-the-grave, foundations, closed panel practices, fixed-fee, and others. If we who believe in fee-for-service do our job, we can successfully compete with any of these schemes. For, in my opinion, we have more to offer the public and the medical profession in terms of predictability of cost and quality of care than any of the alternative systems being experimented with or discussed today.

CONSULTANTS FOR

California Medicine IN 1973

The editors wish to acknowledge with appreciation the valued services, beyond those of members of the Editorial Board, given by the following persons to the Journal during the past year.

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Yatsu, Frank
Yerushalmy, Jacob*

Zielinski, Florian W.

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*Deceased October 15, 1973

CALIFORNIA MEDICAL ASSOCIATION
1856

103rd Annual Session
AND
Western Scientific Assembly

MARCH 2-6, 1974 • HILTON HOTEL • SAN FRANCISCO

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- ☐ 8th ANNUAL CANCER SYMPOSIUM
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- ☐ SPECIAL CONFERENCE
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- ☐ SPECIAL CONFERENCE
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THE COMPLETE ANNUAL SESSION PROGRAM IS
PRINTED FOLLOWING THE VOLUME INDEX ON PAGE 84.

*(For Hotel Reservations see Page 34 of Annual Sessions Program
or Page 36 of Advertising Section)*

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, CA 94102.

Correction

In the November issue of CALIFORNIA MEDICINE Leslie Irwin, MD, of Long Beach was erroneously reported to have died.

⁂

ARBUCKLE, ROBERT K., Redlands. Died October 23, 1973 in Loma Linda, aged 67. Graduate of Temple University School of Medicine, Philadelphia, 1933. Licensed in California in 1938. Doctor Arbuckle was a retired member of the San Bernardino County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

BURTON, THOMAS P., San Francisco. Died October 24, 1973 in San Francisco, aged 73. Graduate of the University of Illinois College of Medicine, Chicago, 1941. Licensed in California in 1941. Doctor Burton was a member of the San Francisco Medical Society.

⁂

CRUDEN, ALEXANDER WESLEY, Ventura. Died September 24, 1973, aged 70. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1930. Licensed in California in 1930. Doctor Cruden was a member of the Ventura County Medical Society.

⁂

DICK, FRANCIS M., Walnut Creek. Died September 18, 1973 in Concord of pneumonia, aged 59. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1946. Licensed in California in 1952. Doctor Dick was a member of the Alameda-Contra Costa Medical Association.

⁂

DJONG, WAYLAND W., San Francisco. Died September 22, 1973 in San Francisco, aged 56. Graduate of Albany Medical College, 1950. Licensed in California in 1951. Doctor Djong was a member of the San Francisco Medical Society.

⁂

ENRIGHT, WILLIAM MICHAEL, San Jose. Died October 1, 1973 in San Jose, aged 63. Graduate of McGill University Faculty of Medicine, Montreal, 1940. Licensed in California in 1947. Doctor Enright was a member of the Santa Clara County Medical Society.

FLUHRER, JOHN JAMES, Alhambra. Died October 24, 1973 in San Gabriel of cancer, aged 54. Graduate of University of Southern California School of Medicine, Los Angeles, 1943. Licensed in California in 1943. Doctor Fluhrer was a member of the Los Angeles County Medical Association.

⁂

FRIEND, WILLIAM KEITH, Santa Ana. Died July 1, 1973 in Orange of coronary artery insufficiency, aged 52. Graduate of University of Southern California School of Medicine, Los Angeles, 1946. Licensed in California in 1947. Doctor Friend was a member of the Orange County Medical Association.

⁂

GRANNIS, WILLIAM R., Palo Alto. Died October 11, 1973 in Palo Alto, aged 55. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1944. Licensed in California in 1948. Doctor Grannis was a member of the Santa Clara County Medical Society.

⁂

HARTENSTEIN, PAUL E., Needles. Died September 20, 1973 in Needles of smoke inhalation in home fire, aged 44. Graduate of Western Reserve University School of Medicine, Cleveland, 1955. Licensed in California in 1958. Doctor Hartenstein was a member of the San Bernardino County Medical Society.

⁂

HERRON, EUGENIA LUCILLE, San Francisco. Died October 6, 1973 in San Francisco of heart disease, aged 72. Graduate of University of California Medical School, Berkeley-San Francisco, 1934. Licensed in California in 1934. Doctor Herron was a member of the San Francisco Medical Society.

⁂

JOHNSON, ELMER H., Los Angeles. Died September 18, 1973 in Los Angeles, aged 93. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, 1919. Licensed in California in 1919. Doctor Johnson was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

MCBRIDE, WILLIAM CRAIG, JR., Palm Springs. Died August 25, 1973 in Palm Springs, aged 73. Graduate of the University of Oregon Medical School, Portland, 1929. Licensed in California in 1929. Doctor McBride was a member of the Riverside County Medical Association.

⁂

MONACO, SALVATORE, Balboa. Died September 9, 1973 in Balboa, aged 80. Graduate of the University of Louisville School of Medicine, 1914. Licensed in California in 1919. Doctor Monaco was a member of the Orange County Medical Association.

PINGER, ROBERT R., Concord. Died October 30, 1973 in Concord, aged 63. Graduate of University of California Medical School, Berkeley-San Francisco, 1939. Licensed in California in 1939. Doctor Pinger was a member of the Alameda-Contra Costa Medical Association.

⁂

PRUC, WLADIMIR, Los Angeles. Died September 3, 1973 of heart disease, aged 63. Graduate of Karl-Franzens-Universität Medizinische Fakultät, Graz, 1942. Licensed in California in 1956. Doctor Pruc was a member of the Los Angeles County Medical Association.

⁂

SCHULZE, FRITZ JOHANN, Berkeley. Died October 18, 1973 in San Pablo, aged 66. Graduate of St. Louis University School of Medicine, 1934. Licensed in California in 1935. Doctor Schulze was a member of the Alameda-Contra Costa Medical Association.

⁂

SUTTERLIN, FREDERICK K., Palm Desert. Died in October, 1973 in Yosemite National Park, aged 70. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1938. Licensed in California in 1938. Doctor Sutterlin was a retired member of the Riverside County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

TEBBETTS, HERBERT E., Whittier. Died October 4, 1973 in Chula Vista, aged 86. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1914. Licensed in California in 1916. Doctor Tebbetts was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

WESTERHOUT, FRITZ CUTHBERT, Manhattan Beach. Died October 16, 1973 in South Bay, aged 68. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1933. Licensed in California in 1933. Doctor Westerhout was a member of the Los Angeles County Medical Association.

⁂

WIEBE, FRANK E., Salinas. Died September 25, 1973 in Salinas of cancer, aged 74. Graduate of The University of Nebraska College of Medicine, Omaha, 1927. Licensed in California, 1929. Dr. Wiebe was a member of the Monterey County Medical Society.

⁂

WILSON, J. DWIGHT, Carmel. Died November 9, 1973 in Carmel, aged 79. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1925. Licensed in California in 1925. Doctor Wilson was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

WILT, FILLMORE MARTIN, Martinez. Died October 2, 1973 in Walnut Creek of heart disease, aged 57. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1943. Licensed in California in 1943. M.D. degree from California College of Medicine, 1962. Doctor Wilt was an associate member of the Napa County Medical Society.

BOOK REVIEWS

California Medicine does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

READINGS IN MODERN SURGERY—Edited by Richard H. Egdahl, MD, Professor and Chairman, Department of Surgery, Boston University School of Medicine; and John A. Mannick, MD, Professor of Surgery, Boston University School of Medicine. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 670 pages, $21.50 (Hardcover), $14.50 (Softcover).

This volume consists of 58 selected papers from current surgical literature. Individual subject headings such as stomach, transplantation, tumors, etc., may be represented by one to five papers. In addition each paper is followed by an overview by the senior author and by an annotated bibliography.

I'm afraid that for the surgeon, the material in this volume is largely repetitive. The articles have previously been published in surgical journals and may have been presented before surgical societies. The same can be said for the articles in the annotated bibliography.

However, this volume may have more to offer the non-surgeon than the surgeon. Students, residents and internists may find it a ready source for current information and thought on diverse surgical problems. In this regard the selection and organization of the subject headings, the overview and annotated bibliography may be especially helpful and would complement information in a standard surgical textbook as intended.

Edward Passaro, Jr., MD

* * *

RESPIRATION IN HEALTH AND DISEASE—Second Edition—Reuben M. Cherniack, MD, Professor of Medicine, University of Manitoba, Director, Joint Respiratory Programme, University of Manitoba, Head, Section of Respiratory Diseases, Winnipeg General Hospital, Director, Respiratory Division, Clinical Investigation Unit, Winnipeg General Hospital, Physician, Winnipeg General Hospital and Rehabilitation Hospital—D. A. Stewart Centre; Louis Cherniack MD, Associate Professor of Medicine, University of Manitoba, Physician, Winnipeg General Hospital and Rehabilitation Hospital—D. A. Stewart Centre; Arnold Naimark, MD, Dean of Medicine, Professor and Head, Department of Physiology, University of Manitoba, Associate Director, Respiratory Division, Clinical Investigation Unit, Winnipeg General Hospital Physician, Winnipeg General Hospital. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1972. 496 pages with 115 illustrations, $14.50.

This volume provides a forthright, compact, well-organized orientation to the field of applied pulmonary physiology where practiced in settings which rely on laboratory-based information for intelligent therapeutic action. Accordingly, it would be of value to the practitioner, house staff officer, or student. The volume is based on the considerable research and practical experience of its three authors, all respected scientists in their own rights, with assistance in the pediatric area from Victor Chernick, M.D., Professor of Pediatrics at the University of Manitoba. It is broad in scope, covering the vast majority of subjects that are of current interest in the field of respiration. As such, some subjects of importance are treated too briefly, such as the discussion of mechanisms underlying hypoxia, but in general the overview is timely. The sections on the pulmonary circulation, respiratory control mechanisms, the aging lung, neonatal pulmonary physiology and exercise physiology are as sound as any I have read. The book covers in sufficient detail newer tests of considerable importance, such as frequency-dependence of compliance, "closing volumes," and immune secretory globulins. The book would be specially useful to students in respiratory therapy and cardiopulmonary technology, a well as for quick review by house officers before entering formal postdoctoral training in the various pulmonary specialties.

Another outstanding attribute of this book is its easily readable style. The sections on pulmonary mechanics, blood gas analysis and physical diagnosis of the chest are particularly delightful in the style with which they are written.

With all these "pluses," it is disturbing to note that several errors in the script, some of them quite misleading, have been carried over from the first to the current, second edition. The majority, but not all of these errors are simple typographical ones, or mistakes in notation or orientation of the figures. Other errors, such as the concept that maintenance of an arterial PO_2 of 80-100 mm Hg. is necessary in the average patient, are grossly misleading in the terms of current physiologic thinking.

Still, all in all, in a relatively arid literary wasteland where the usual introduction to clinical pulmonary physiology is more often a treatment than a "treat," the volume is a welcome addition, which can only be improved by careful editing in its next edition.

George G. Burton, MD

* * *

DISEASES OF THE BREAST—Second Edition—C. D. Haagensen, MD, Professor Emeritus of Clinical Surgery, The College of Physicians and Surgeons, Columbia University. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1971. 829 pages with 578 illustrations, $35.00.

The Second Edition of *Diseases of the Breast* is the most comprehensive and informative, and definitive work in its field.

Dr. C. D. Haagensen has brought his monumental first edition up-to-date, covering every aspect of diseases of the breast in a most authoritative fashion. Anatomy, physiology, pathology, and treatment are presented in a very readable, and yet very comprehensive fashion.

This book should be in the hands of every physician or surgeon who deals with diseases of the breast.

Dr. Haagensen takes up the controversial issue of how extensive surgical extirpation should be for cancer of the breast. He rigidly adheres to his time honored, classical radical mastectomy, and states with clarity and persuasion his conviction that there is no place for lesser operations. In this respect, despite identical clinical findings, Dr. Haagensen gives no consideration to the extreme biological variation in different cancers of the breast. The recent studies with newer isotopes indicate that a significant number of patients with clinical stage-I cancer of the breast have, in fact, bony metastases. It is obvious that the most radical local operation will not result in cure, and in this area certainly consideration to lesser mutilating operation must be given.

Dr. Haagensen's persuasive support of the standard radical mastectomy is based on an abiding faith that most cancers of the breast are local growths. It seems likely to this reviewer that the next decade will produce evidence that the enormous biological variations in cancer of the breast will require therapy specifically designed for each particular patient. Increasing use of a modified radical operation, which if properly done, can be as complete as in the standard radical, is indicative of the changing mood of the medical profession in regard to this disease.

Despite the above comments, Dr. Haagensen's book will remain as one of the finest, most informative, and authoritative books in its field. The facts are there in abundance for all to read. Interpretation of these facts will remain an area of controversy until new methods for precise elucidation of the biological variations of each individual cancer become available.

J. Engelbert Dunphy MD

* * *

RENAL DISEASE IN CHILDHOOD—Second Edition—John A. James, MB (Edin.), MRCP, DCH, Professor of Pediatrics, Department of Pediatrics, University of Southern California School of Medicine, Chief Physician, Pediatric Pavilion, Los Angeles County/USC Medical Center, Los Angeles. The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, MO (63141), 1972. 377 pages, $23.50.

Dr. James' second edition of his book *Renal Disease in Childhood* is directed to the "non-nephrologist." He has written a useful book that will assist practicing physicians, housestaff, and students in understanding kidney disease in patients.

The sections describing disease entities are the book's strongest. The descriptions are short, clear and specific. Treatment, especially drug treatment is dealt with in a direct and useful manner, the tables are helpful. The author often invokes his own opinion in a pleasant way to provide a recommendation where no definitive statement is possible.

The discussion of physiology is less effective. The need for brevity precludes an in-depth discussion. The dilemma of all pediatric books is having to deal with the variables of age and size, be comprehensive in a subject and still be concise. Neither renal physiology nor body fluid physiology is dealt with authoritatively and the reader should depend on other sources, as the author, himself, seems to imply.

The sections on repeated urinary tract infections in girls appropriately develop the evidence of pro and con as to their potential for leading to renal failure. The author comes down on the side that renal failure rarely results; simple bacteremia may not be a major medical problem. This view heretical a short time back, is now gaining respectability.

His descriptions of nephrosis and glomulonephritis are also excellent. We disagree that the mechanism for edema in acute nephritis and nephrosis is the same, but overall the presentations are very useful.

The book can be recommended to its intended audience.

Malcolm A. Holliday, MD

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RHEUMATIC FEVER—Second Edition—Volume II in the Series Major Problems in Clinical Pediatrics—Milton Markowitz, MD, Professor and Head, Department of Pediatrics, University of Connecticut School of Medicine, Farmington, Connecticut; and Leon Gordis, MD, Dr PH, Associate Professor of Epidemiology and of Medical Care and Hospitals, Johns Hopkins School of Hygiene and Public Health, and Associate Professor of Pediatrics, Johns Hopkins School of Medicine, Baltimore, Maryland. Alexander J. Schaffer, Consulting Editor. W. B. Saunders Company, Publisher, West Washington Square, Philadelphia, Pa. (19105), 1972. 309 pages, illustrated, $11.50.

The incidence of rheumatic fever has markedly declined in the past few decades; in our own state the disease has become distinctly uncommon. It has not disappeared, however, and the physician confronted with clinical problems in this field more than ever needs to refresh and update his own knowledge about rheumatic fever. From its first publication in 1965, Dr. Markowitz and Dr. Kuttner's book on this subject has been the outstanding reference in its field. As Dr. Anne Kuttner has passed away, the second edition is prepared by Drs. Markowitz and Leon Gordis. This new edition has been rewritten to include the new studies and advances in rheumatic fever and in the biology of the streptococcus, including the work of Fox and Kaplan on the development of streptococcal vaccine and Wannamaker's studies concerning the difference between the biology of streptococcal skin and throat infection. The references have been extensively revised and updated. The book contains sixteen chapters dealing with such topics as the biology of the streptococcus, the etiology, the pathology, diagnosis, course, treatment and prevention of rheumatic fever. The chapter on primary prevention deals with the diagnosis and management of streptococcal infection and streptococcal carriers. There are also three appendices, embodying the American Heart Association 1971 statements on the Jones Criteria for the Diagnosis of Rheumatic Fever, and on the prevention of the disease. A statement prepared by Dr. Lewis Wannamaker on the technique of obtaining a throat culture, streaking, reading, confirming and interpreting the results of the culture, is also included. The authors review the accumulated evidence in the literature, clearly present the controversial nature of some of the evidence, yet in the end, come out with their own clear cut recommendations which are of value to the reader. Their advice is particularly apparent and appreciated in the discussion about the use of steroids and aspirin in the treatment of rheumatic fever.

In summary, this is an authoritative and readable up-to-date discussion of all aspects of rheumatic fever for the clinician. It should be made available on the shelf of hospital and medical libraries as a reference. Those physicians who are particularly interested in rheumatic fever as a subject or see more than a very occasional patient with this disease will want to have this book available in their personal library.

M. Grossman, MD

* * *

BONE TUMORS—Fourth Edition—Louis Lichtenstein, MD, Clinical Professor of Pathology, University of California, San Francisco; Professor Extraordinario, National University of Mexico. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. (63103), 1972. 441 pages, 496 illustrations in 252 figures, $24.50.

The usefulness and popularity of this work has been well demonstrated in the 20 years since the 1st edition. Now a new 4th edition has been published. The printing format is more legible, and the number of illustrations, chiefly radiographs, has been modestly increased.

Dr. Lichtenstein is one of the true giants in the field of bone tumors. In his own works or with collaborators like Jaffee we can follow the evolution of modern knowledge of bone pathology. From a confusing mass of anecdotal material he helped develop many of our current concepts. His name is intimately associated with a wide range of neoplastic and non-neoplastic bone conditions such as giant cell tumor, non-osteogenic fibroma, solitary cyst, chondroblastoma, chondromyxoid fibroma, aneurysmal bone cyst, chondrosarcoma, villonodular synovitis and others. This book is his testament.

It is a very personal book, a true monograph, written sharply and to the point. The style contrasts greatly with the thorough but rather dull multi-authored tomes now in fashion in medical literature. Because the text is short, the narrative frequently is somewhat dogmatic and avoids presenting alternative points of view in areas of controversy. One such area is the prognostic value of histologic grading of giant cell tumors. However, this drawback does not detract from the usefulness of this book, especially to residents and younger physicians. This is not a book one can refer to to for a discussion of modern biochemical concepts; rather it is the distillation of a lifetime of experiences with bone tumors.

There is little new in this edition, except for a brief chapter on certain rare primary tumors of bone such as leiomyosarcoma and malignant mesenchymoma. There is also a change in the concept of the unusual tumors called adamantinoma of bone. Dr. Lichtenstein thinks these represent dermal inclusion tumors from embryonic rests.

I would not recommend that one buy the new edition if one already owns a copy of the previous volume since there is little change and the new price is 50 percent higher than the last.

I would, however, recommend a re-reading of the introduction which remains as important and relevant today as when it was first written over 20 years ago. In this introduction, Dr. Lichtenstein discusses the clinical management of bone lesions that may be tumors and his sound advice should be heeded by the orthopedic surgeon, radiologist, pathologist or any physician faced with the problem of possible bone tumor in his patient.

DOUGLAS J. SHEFT, MD

* * *

GASTROINTESTINAL ANGIOGRAPHY—Volume I in the Series: Saunders Monographs in Clinical Radiology—Stewart R. Reuter, MD, Professor of Radiology, University of Michigan School of Medicine, Ann Arbor; Director, Department of Radiology, Wayne County General Hospital; Helen C. Redman, MD, Assistant Chief, Department of Radiology, Mt. Zion Hospital, San Francisco; Clinical Associate Professor of Radiology, University of California, San Francisco, and Stanford University School of Medicine. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1972. 292 pages, with 482 illustrations, $17.00.

Gastrointestinal Angiography is a concise yet thorough review of a rapidly expanding new field. The material is logically divided into ten chapters. The first chapter deals with equipment and technique used in catheterization. It leads the less experienced radiologist through the steps of puncture, introduction and manipulation of the catheter, and the more common pitfalls and difficulties. The second chapter deals scholarly and exhaustively with anatomy.

Chapters III through VIII deal with pathologic entities in which angiography is used. The material is abundantly illustrated and the quality of the illustrations is excellent. The chapter on pharmacoangiography is up-to-date and discusses vasoconstrictor drugs, vasodilator drugs and their uses in angiography; there is a separate subchapter on therapeutic pharmacoangiography for tumor infusion, control of gastrointestinal hemorrhage, delivery of thrombogenic material, and the use of vasodilators in splanchnic vasoconstriction.

The book reads easily and should be of great value for anyone who wishes to learn more about gastrointestinal angiography.

The authors speak about complications from the various procedures as they deal with various techniques and conditions, rather than have a separate chapter on complications, ways to prevent them and coping with them once they occur.

This book fills a need and will undoubtedly find its way to the shelves of everyone performing angiography.

ALEXANDER R. MARGULIS, MD

* * *

THE CHINESE VERSIONS OF MODERN ACUPUNCTURE—Translated from the Chinese and with an Introduction by Henry C. Lu, PhD. Academy of Oriental Heritage, Office 308, Ford Building, 193 E. Hastings St., Vancouver 4, B.C., Canada, 1973. 241 pages, $40.00.

During the past year there has been a tremendous outpouring of English texts available to the American public concerning acupuncture. Much of what is written is anecdotal or repetitious, since there are very few original sources upon which authors may base their works.

Dr. Lu has compiled his book from primarily 3 sources. One is the classic of acupuncture, which is one of 2 volumes of the *Yellow Emperor's Book of Internal Medicine*. This work has been previously translated, quoted and interpreted by a number of authors and the present work adds litte to what was previously available. For a major portion of his text, however, Dr. Lu draws upon materials prepared in 1970 and 1971 by special committees in Northern and Southern China and published for the instruction of modern acupuncturists. With this as a basis, Dr. Lu's text becomes one of the few available to the English reader, describing acupuncture as it is currently practiced in the Peoples' Republic of China.

A chapter on techniques of acupuncture includes a description of the needles used, postures to be taken by the patient, methods of locating acupuncture points, as well as techniques of needling used for various circumstances. A section concerned with technical problems which may be encountered is a welcome addition to what has previously been available in the literature. One procedure described is the massaging of the patient's philtrum to relieve fainting which may occur during treatment.

In a section describing the specific locations of the various acupuncture points the author goes to great efforts in attempts to resolve the differences present in the Northern and Southern Chinese texts. This often makes the references to points cumbersome, but since this section is amply illustrated, and the Chinese transliteration of the point name accompanies the meridian name and number, these problems are able to be overcome. Separate chapters on the special points of the hand and ear are also included. This information was previously very difficult to obtain in English and supplies detailed information of these very important point locations.

A description of acupuncture anesthesia is excellent. Not only does the author give the history of acupuncture anesthesia and the rationale behind the needle placements, there is also included a listing of the specific acupuncture points for various surgical procedures. This specific information was unavailable to the Western reader until very recently.

Although not as encyclopedic as some other similar listings, the author has chosen to use Western terminology classification in a section on diseases amenable to treatment by acupuncture. For this reason it becomes much more useful to those practitioners familiar with Western medicine. Points used for the treatment of angina pectoris, bronchitis or cholecystitis, for example, can be easily learned.

The major criticism of this book is in the technical aspects of the printing and layout. It is apparently done by mimeograph duplication, or very poor quality photo offset. Although most of the text is legible, there are some parts that are difficult to decipher, due to variation in the printing quality. Because of these technical points, it would seem that the rather expensive price of this volume is unjustified.

ANDREW J. LEWIN, MD

* * *

ACUPUNCTURE THERAPY—Current Chinese Practice—Leong T. Tan, MD, practicing urologist, San Francisco; Margaret Y.-C. Tan, MS, Associate Specialist, Department of Medicine, University of California, San Francisco, and trained acupuncturist; Ilza Veith, PhD, Professor and Vice Chairman, Department of Health Sciences, University of California, San Francisco. Temple University Press, Philadelphia (19122), 1973. 159 pages, $15.00.

The recent resurgence of interest in acupuncture in Western countries, especially the United States, is reflected by the large number of publications in English, which have recently come on the market. Many of these publications have merely rehashed the ancient Chinese philosophy upon which acupuncture is based, as well as reporting the technique and results of Western practitioners.

Acupuncture as practiced in China today is in many ways different from that practiced in ancient times. By basing their work on Chinese texts currently in use, the authors bring to an English audience many of the refinements of technique which were previously unavailable.

The major portion of the book is devoted to the technical aspects of acupuncture therapy. Detailed descriptions of acupuncture needles and the techniques of needle insertions are extremely valuable. Although these techniques are fairly straightforward, several tricks are explained, which will enable the acupuncturist to perform his therapy with a minimum amount of patient discomfort.

A general description of the method used to locate acupuncture points is concise, informative and easily understandable. These explanations are accompanied by detailed drawings, which enable the reader to easily follow the text. In addition to the details for locating each point, indications for its use and specific techniques of needle insertion are described. Because of the attention to detail in the written text and diagrams, this book is superior to most of those currently available and enables even the relatively uninitiated to locate many acupuncture points without too much difficulty.

A chapter explaining some of the details of acupuncture anesthesia contains a great deal of information, which was previously available only in Chinese. The authors explain that the acupuncture locations are divided into body points, ear points and nose points. By using points from each location, analgesia sufficient for surgery is obtained. Details of needle placement for specific operative procedures are also given.

A short chapter on diseases and symptoms amenable to acupuncture therapy gives a good description of the general principles involved in the choice of points, both in the local area as well as at distant sites. Although a section on acupuncture points used for the treatment of specific symptoms is also included, this is extremely brief and incomplete and the interested reader would do better by referring to other available English texts.

A major shortcoming of this work is that the authors have chosen not to follow the Western practice of labeling each point by its meridian name and sequential number. Although with this Western nomenclature there are minor discrepancies between authors in the naming and numbering of acupuncture points, it certainly facilitates the locating of acupuncture points for the Western reader. The authors have chosen to use only the English transliteration of the Chinese name for each point which, while avoiding these minor variations, does increase the difficulty of trying to systematize the locations.

ANDREW J. LEWIN, MD

* * *

BRONCHOPULMONARY DISEASES AND RELATED DISORDERS—Volumes 1 and 2—Editors: Cranston W. Holman, MD, Clinical Professor of Surgery, Cornell University Medical College, Attending Surgeon, The New York Hospital-Cornell Medical Center, New York City; Carl Muschenheim, MD, Clinical Professor of Medicine, Cornell University Medical College, Attending Physician, The New York Hospital-Cornell Medical Center, New York City. Harper & Row, Publishers, Inc., Medical Department, 2350 Virginia Avenue, Hagerstown, MD (21740), 1972. 1,035 pages in 2 volumes, $60.00.

This text book on bronchopulmonary disease is quite unusual in its approach by being very practically oriented and is to be recommended on this basis. It is a very functional book with a good deal of material related to direct patient care and is therefore particularly well-oriented toward practitioners.

As is the case of any multiple-author book, there is a good deal of variation in the quality of the presentation from chapter to chapter. However, by and large it is a good book and very up to date in most areas, with a much greater emphasis on therapy than most texts. The chapters are generally written by experts in their own specific fields and for this reason are generally well-organized and, very importantly, have extensive bibliographies for further reading. The text is not as exhaustive as some others with respect to the areas traditionally covered, but fully 20 percent of the two volumes is devoted to special diagnostic procedures and surgical techniques, much of which is not readily available in other comparable texts. This is due in part to its drawing more than the usual amount from surgery and related disciplines such as anesthesiology, pathology, otolaryngology and epidemiology. Illustrations are generally well-selected and well-correlated with the text.

In general this should be considered a good general text and stepping stone to further reading for the internist and surgeon involved in care of patients with pulmonary disease and for medical students and post-graduate trainees.

DANIEL H. SIMMONS, MD, PH D
STANLEY M. CASSAN, MD, PH D

* * *

FUNCTIONAL AIDS FOR THE MULTIPLY HANDICAPPED—Edited by Isabel P. Robinault, PhD, Supervisor, Research Utilization Laboratory, ICD Rehabilitation and Research Center, New York City; Formerly Coordinator, Professional Activities, United Cerebral Palsy Associations, Inc., New York City. Harper & Row, Publishers, Inc., Medical Department, 2350 Virginia Avenue, Hagerstown, Md. (21740), 1973. 256 pages with 300 illustrations, $10.00.

This is an excellent book of assistive devices for the handicapped child. It is primarily geared for the child with severe spasticity, athetosis and dystonia but it will serve for other disabilities as well.

Each device is illustrated with a narrative on its construction with actual measurements, the type of materials used and some very useful hints on variations to meet individual needs. The details are presented so clearly that one need not be a carpenter or have affinity for mechanical skills in order to construct one. For those that may want to purchase these devices, commercial sources are listed. Needless to say, the indications for these devices are spelled out with emphasis on making maximum use of the individual's abilities.

The book is divided into 4 chapters covering: (1) transfer, travel and mobility; (2) personal care; (3) communications and learning; and (4) recreation. In addition, there is an Appendix that lists the sources of all the leading providers of "aids and information."

I am very pleased to recommend this book without any reservations to all personnel involved with the medical rehabilitation process.

GREGORY BARD, MD

* * *

HANDBOOK OF PEDIATRICS—Tenth Edition—Henry K. Silver, MD, Professor of Pediatrics, University of Colorado School of Medicine, Denver; C. Henry Kempe, MD, Professor of Pediatrics and Chairman, Department of Pediatrics, University of Colorado School of Medicine; and Henry B. Bruyn, MD, Clinical Professor of Pediatrics and Medicine, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA 94022. 694 pages, $6.50.

The continued popularity of this handbook is demonstrated by it now achieving its tenth edition and by its translation into eight foreign languages.

A perusal of the book continues to justify this popularity.

It contains a wealth of useful information and its small size makes it practical for fitting into a coat pocket or a medical bag. House officers and practicing physicians should both find it a useful source of on the spot information.

WILLIAM C. DEAMER, MD

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PROGRAM

CALIFORNIA MEDICAL ASSOCIATION

103rd
Annual Session
and
3rd Western Scientific Assembly

March 2-6, 1974

Hilton Hotel San Francisco

- ✓ Scientific Section Programs
- ✓ Special Conferences
- ✓ Scientific and Technical Exhibits
- ✓ Meetings of the House of Delegates

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ACKNOWLEDGMENT

The Committee on Scientific Assemblies is indebted to the members of the Advisory Panels to the Scientific Sections for their work in helping plan and continually improve the educational quality of the Annual Scientific Assembly.

These twenty-one panels, each a blue-ribbon body representing its specialty, have increasingly contributed to the unique educational programs of the California Medical Association.

On behalf of all the members of California Medical Association and particularly the Committee on Scientific Assemblies and the Section Program Planners, I would like to thank the 360 members of the Advisory Panels for their valuable participation.

ALBERT D. HALL, MD, *Chairman*
Committee on Scientific Assemblies
of the Scientific Board

IMPORTANT ELECTION NOTICE TO ALL CMA MEMBERS

As a CMA member, you are a voting member of one of the 21 scientific specialty sections. The scientific program of each section includes a *business meeting to elect officers of the section*. These three officers—chairman, secretary, and assistant secretary—will be your representatives on the Advisory Panel to speak for you on scientific and educational issues of vital concern to your specialty: planning programs of continuing medical education; questions and controversies of acceptable medical practice; evaluation of proposed legislation, and the publication of "Epitomes of Progress" for *California Medicine*. These three officers also make nominations to the Scientific Board.

Make your voice heard in these important areas by participating in the business meeting and voting for the officers of your section. See your section program for time and place.

Information

PLEASE NOTE

Unless otherwise indicated, all meetings will take place at the Hilton Hotel.

BADGES

It is important that badges be worn at all times. Admission to all meetings and exhibits is by badge only.

COUNCIL

The Council will meet on Friday; time and location to be announced. Executive sessions will be posted on the hotel schedule boards.

HOUSE OF DELEGATES

For meeting times, places and agenda—see page 30. The list of Delegates and Alternates appears on pages 28 and 29.

EMERGENCY CALLS AND MESSAGES

Convention Emergency Call Number—**(415) 441-5845**

1:00-5:00 pm, Friday, March 1

9:00 am-5:00 pm, Saturday, March 2 through Wednesday, March 6

MESSAGE CENTER

Provided through the courtesy of Pacific Telephone Company.

(415) 441-5845
East Lounge, Ballroom level
Hours: 9:00 am-5:00 pm

The Association will attempt to transmit emergency messages to individual physicians. Each physician should notify his own office of the exact times and locations of meetings he plans to attend.

Routine Messages will be kept at the Message Center in the East Lounge, Ballroom level.

Physicians are requested to check with the Message Center at least once daily.

INDEX TO PARTICIPANTS

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EXHIBITS

Technical Exhibits are located in the Imperial Ballroom and Franciscan Room. Scientific and Organizational Exhibits are located in the Garden Lane, California Room and North Lounge.

INFORMATION DESK

The information desk will be located in the West Lounge, near the CMA Registration Booth, and will be open daily from 9:00 am to 5:00 pm, Saturday, March 2 through Wednesday, March 6.

REGISTRATION

Registration will take place in the West Lounge, Hilton Hotel, starting Friday, March 1 at 1:00 p.m. Saturday through Tuesday registration will begin at 8:00 a.m.

All members, guests and visitors are requested to register immediately on arrival.

There will be a $10.00 registration fee for attendees who are not CMA members.

In addition to CMA members, the following individuals will be exempt from the registration fee: CMA members' spouses and families; medical students and interns; students of other health professions; program participants and medical executives.

Admission to the conferences and section meetings, as well as to the exhibit area, is by badge only.

Members wishing to vote in specialty sections must indicate the appropriate section when registering; voting in other sections will not be allowed.

QUALIFICATIONS/REQUIREMENTS FOR REGISTRATION

All MDs with credentials showing that they hold a valid license to practice medicine (e.g., membership card in CMA, AMA or county medical society).

Medical students, upon presentation of credentials from their medical schools, letters from dean's office, or membership card in CMA, AMA or SAMA.

Medical assistants upon presentation of letter from a physician-employer or AAMA membership card.

Military paramedical personnel upon presentation of a letter from their commanding officer.

Dentists (DDS); Doctors of Veterinary Medicine (DVM); registered nurses (RN); student nurses, x-ray technicians; allied public health personnel and others will be admitted provided they have proper identification.

ALL QUESTIONS ON ADMISSION will be passed upon by a member of the Committee on Registration present at the desk.

SPECIAL ANNOUNCEMENT

Each scientific program which is acceptable for Category I credit toward CMA's Certification in Continuing Medical Education is so designated:

Acceptable for Category I Credit under the CMA Certification Program

The majority of the other educational and scientific programs are acceptable for informal credit.

Physicians should report on the Certification Reporting form the number of program hours attended. Forms and further information are available at the CMA Continuing Medical Education Booth in the exhibit area. Plan to stop by.

Out of State Guests

SPECIALTY SECTION MEETINGS

Allergy

Jerome Glaser, MD, Rochester, New York
Clinical Professor Emeritus, Pediatrics, University of Rochester School of Medicine and Dentistry

Frederic Speer, MD, Shawnee Mission, Kansas
Clinical Professor, Pediatrics, University of Kansas

Anesthesiology and Chest Diseases

Edward A. Gaensler, MD, Boston
Professor of Surgery, Harvard University Medical School

General Surgery

Rupert B. Turnbull, Jr., MD, Cleveland
Head, Department of Colon and Rectal Surgery, Cleveland Clinic Foundation

Neurology/Orthopedics/Physical Medicine

Roger W. Gilliatt, MD, London

George H. Kraft, MD, Seattle

Obstetrics and Gynecology

John T. Queenan, MD, Louisville
Professor and Chairman, Department of Obstetrics and Gynecology, University of Louisville, School of Medicine

Julian P. Smith, MD, Houston
Associate Professor, Gynecology, University of Texas, M. D. Anderson Hospital and Tumor Institute

Ophthalmology

David L. Knox, MD, Baltimore
Associate Professor, Ophthalmology, Wilmer Ophthalmological Institute, Johns Hopkins Hospital

Otolaryngology

Mr. Dan Adair, Portland
Safety Engineer; Vice-President for Field Operations, Hearing Conservation Noise Control Inc.; Past President, Veterans of Safety International

J. Howard Bunn, Jr., Esq., Raleigh, North Carolina
Chairman, Industrial Commission; Member, Subcommittee on Medical Aspects of Noise and Hearing, American Council of Otolaryngology

Joseph P. Sataloff, MD, Philadelphia
Professor, Otolaryngology, Jefferson Medical College, Thomas Jefferson University; Secretary, American Board of Occupational Hearing Conservation

Preventive Medicine and Public Health

Saul Krugman, MD, New York City
Professor and Chairman, Department of Pediatrics, New York University School of Medicine; Chairman, Committee on Viral Hepatitis, National Research Council

Radiology

Ross E. Brown, MD, Oklahoma City
Associate Professor, Radiological Sciences (Ultrasound), University of Oklahoma Medical Center

SPECIAL CONFERENCES

Alcoholism/Drug Dependence

Frank L. Iber, MD, Baltimore
Professor of Medicine and Chief of Gastroenterology, University of Maryland School of Medicine; Former Medical Director, Boston Alcoholism Detoxification Project

Cancer Symposium

Bernard Fisher, MD, Pittsburgh
Professor of Surgery, University of Pittsburgh, School o Medicine; Editoral Board, **Cancer**; Consultant, National Cancer Institute

Robert V. P. Hutter, MD, Newark, New Jersey
Professor, Department of Pathology, College of Medicine an Dentistry of New Jersey

Eleanor Montague, MD, Houston
Radiotherapist and Professor of Radiotherapy, University o Texas M. D. Anderson Hospital and Tumor Institute; Member, National Breast Cancer Task Force (1969-1972)

Lionel Schour, MD, Bethesda, Maryland
Senior Investigator, Surgical Branch, National Cancer Institut

Jerome A. Urban, MD, New York City
Associate Clinical Professor of Surgery, Cornell Universit Medical College

VD Task Force

Stephanie D. Radford, R.Ph., Hoquiam, Washington
Registered Pharmacist, Health Educator; Chairs Washingto State Pharmaceutical Association VD Education Committe Member of American Pharmaceutical Association

Gloria Steinem, New York City
Editor, *MS* Magazine; Studied for a year in India on Cheste Bowles Asian Fellowship; Graduated Phi Beta Kappa an magna cum laude, Smith College; Named *McCall's* Woma of the year, 1971

King K. Holmes, MD, Seattle
Assistant Professor of Medicine, University of Washingto Consultant, Venereal Disease, World Health Organization

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Special Conferences

Federated Meeting

Regional Meeting

AMERICAN COLLEGE OF PHYSICIANS

Northern California and Nevada

Cosponsored by

CMA SECTION ON INTERNAL MEDICINE

Registration Fee $20
See registration form on Page 25

FRIDAY, MARCH 1 — Colonial Room, St. Francis Hotel

2:00 **Registration**

1:50 **Welcome**
Maurice Fox, MD, Palo Alto

RECENT DEVELOPMENTS IN MYOCARDIAL INFARCTION
Moderator: Howard F. Morrelli, MD, San Francisco

2:00 **Therapy of Cardiogenic Shock in Myocardial Infarction**
William Parmley, MD, Los Angeles

2:30 **Therapy of Arrhythmias in Myocardial Infarction**
Melvin Scheinman, MD, San Francisco

3:00 **Question and Answer Period**

3:10 Break

3:30

CURRENT DEVELOPMENTS IN DERMATOLOGIC DIAGNOSIS AND THERAPY
Moderator: Howard I. Maibach, MD, San Francisco

3:40 **Drug Induced Photosensitivity: A Common Problem**
John H. Epstein, MD, San Francisco

3:50 **An Emergency Life Threatening Dermatosis: Epidermal Necrolysis**
Ervin H. Epstein, Jr., MD, Oakland

4:00 **Psoriatic Nail Arthropathy**
Eugene M. Farber, MD, Palo Alto

4:10 **Medical Aspects of Lues: Gastric Crisis, Hepatitis and Nephrosis**
Marcus A. Conant, MD, San Francisco

4:20 **Cutaneous Hypo and Hyperpigmented Macules in Diagnosis of Systemic Disease**
David L. Cram, MD, San Francisco

4:30 **Vitamin E and Thee**
Rees B. Rees, Jr., MD, San Francisco

4:40 **Nuances in Diagnosis of Reactive Serologic Test for Syphilis**
Denny L. Tuffanelli, MD, San Francisco

4:50 **Fads and Fashions in Contact Dermatitis: 1974**
Howard I. Maibach, MD, San Francisco

5:00 Social Hour

Acceptable for Category I Credit under the CMA Certification Program

SATURDAY MARCH 2 — Colonial Room, St. Francis Hotel

THYROID DISEASE
Moderator: Francis S. Greenspan, MD, San Francisco

8:30 **Diagnostic Techniques in Thyrotoxicosis**
Sidney Ingbar, MD, San Francisco

9:00 **Newer Concepts in the Pathogenesis and Therapy of Grave's Ophthalmopathy**
Joseph P. Kriss, MD, Stanford

9:30 **Thyroid Nodules and Thyroid Cancer**
Francis S. Greenspan, MD, San Francisco

10:00 **Discussion**

10:15 Break

10:45 **Topic to be announced**

11:30 **Presentation by Official College Representative of the American College of Physicians**

12:00 **Luncheon** with Faculty from Stanford University, School of Medicine and University of California, School of Medicine, San Francisco

FATS AND SUGAR
Moderator: Lawrence V. Basso, MD, Palo Alto

1:30 **A Declassification of the Hyperlipidemias**
Gerald Reaven, MD, Stanford

1:55 **The Hypoglycemia Problem**
Maurice Fox, MD, Palo Alto

2:20 **Oral Hypoglycemic Agents, 1974**
Henry Bourne, MD, San Francisco

2:45 Break

HEMATOLOGIC PROBLEMS
Moderator: Robert A. O'Reilly, MD, San Jose

3:15 **Common Anemias Seen by Internists**
Ralph O. Wallerstein, MD, San Francisco

3:40 **Defects in Red Blood Cell Metabolism, Intracorpuscular Defects Resulting in Hemolysis**
Stanley Schrier, MD, Stanford

4:05 **Disseminated Intravascular Coagulation**
William P. Creger, MD, Palo Alto

4:30 **Question and Answer Period**

SATURDAY, MARCH 2 **Ballrooms 5, 6**

Human Sexuality and Its Medical Complications

Chairman and Moderator
David D. Sachs, MD, San Francisco

Presented by
CMA Task Force on Venereal Disease

Cosponsored by
American Public Health Association, Western Regional Office
American Social Health Association
Bay Area Venereal Disease Association
California Academy of Preventive Medicine
California Pharmaceutical Association,
Academy of Community Practice
California Venereal Disease Controllers Association
CMA Committee on School and College Health
CMA Sections on Dermatology
General and Family Practice
Obstetrics and Gynecology
Preventive Medicine and Public Health

Reservation fee: $25.00
Please use reservation form on Page 25

8:30	**Registration**
9:00	**Clinical Gonorrhea** King K. Holmes, MD, Seattle, Washington
9:35	**Asymptomatic Gonorrhea and Techniques of Office Culturing** Frank Cline, Jr., MD, Santa Barbara
9:55	**Neonatal Gonorrhea, Inclusion Conjunctivitis and Reiter's Syndrome** Chandler R. Dawson, MD, San Francisco
10:15	**Question and Answer Period**
10:40	Coffee Break
11:00	**Legislative Problems Relating to Sexuality** Hon. Willie L. Brown, Jr., San Francisco California State Assemblyman
11:30	**Homosexuality: A Way of Loving** Ronald Lee, MSW, San Francisco
12:00	**Question and Answer Period**
12:15	Luncheon
1:00	**Women as Patients** Gloria Steinem, New York City
1:45	**Syphilis** Marcus Conant, MD, San Francisco
2:15	**Specific Female Medical Complications** N. Edward Boyce, Jr., MD, San Francisco
2:45	**Other Medical Complications** Marcus Conant, MD, San Francisco
3:15	**Question and Answer Period**
3:35	Coffee Break
3:50	**The Physician's Role in Prevention** Warren Ketterer, MD, Sacramento
4:05	**Current Condom Concepts** Stephanie Radford, RPh, Hoquiam, Washington
4:35	**Contraception and Sexuality** Sadja Goldsmith, MD, San Francisco
4:55	**Question and Answer Period**

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the CMA Certification Program

SATURDAY, MARCH 2 **Ballroom 4**

EIGHTH ANNUAL CANCER SYMPOSIUM

The Breast Cancer Dilemma Mountain or Mole Hill

Chairman: Robert J. Schweitzer, MD, Oakland

Cosponsored by
CMA Committee on Cancer
American Cancer Society, California Division
Alameda, Contra Costa, San Francisco
San Mateo and Santa Clara Units

2:00	**New Developments in Early Detection and Diagnosis** Lionel Schour, MD, Bethesda, Maryland
2:25	**Pathology of Breast Cancer and Its Clinical Significance** Robert V. P. Hutter, MD, Newark, New Jersey
2:50	**Radiation Therapy of Operable Cancer** Eleanor Montague, MD, Houston, Texas
3:15	**Lumpectomy and Partial Mastectomy** Bernard Fisher, MD, Pittsburgh, Pennsylvania
3:40	**Selection of Surgical Procedure for Operable Cance** Jerome A. Urban, MD, New York City
4:05	**Panel Discussion**
4:55	**Closing Remarks and Adjournment**

SATURDAY, MARCH 2 **Rosewood Suit**

Treatment and Prevention of Pesticide Poisoning

Chairman: Robert S. Hockwald, MD, San Francisco

Presented by
CMA Committee on Occupational Health

TOXICOLOGY AND TREATMENT

Moderator: Ephraim Kahn, MD, Berkeley

2:00	**Classification and Toxicology of Pesticides** Thomas H. Milby, MD, Berkeley
2:20	**Diagnosis and Treatment of Organophosphate and Carbamate Poisoning** Robb Smith, MD, Orange Cove
2:40	**Diagnosis and Treatment of Other Pesticide Poisoning** Charles Hine, MD, San Francisco
	Question and Answer Period

PREVENTION OF PESTICIDE POISONING

Moderator: Irving R. Tabershaw, MD, Berkeley

3:00	**Farmworker Exposure to Pesticide Residues** Ephraim Kahn, MD, Berkeley
3:20	**The Primary Physician and Occupational Health Practice** Hector Blejer, MD, Los Angeles
3:40	**Medical Supervision of Pesticide Workers** B. Dwight Culver, MD, Irvine
	Question and Answer Period

SUNDAY, MARCH 3 **Ballroom 4**

Alcoholism and Drug Dependence: Medical Problems and Socio-political Issues

Chairmen
Jack D. Gordon, MD, San Francisco
Arthur Bolter, MD, San Leandro

Sponsored by
MA Committee on Alcoholism and Other Drug Dependence

Cosponsored by
University of California, San Francisco, School of Medicine

Reservation Fee: $15.00
Please use reservation form on Page 25

Moderator: Jack D. Gordon, MD, San Francisco

8:45 **Early Recognition and Management of Alcoholism in Medical Practice**
Basil B. Clyman, MD, Los Angeles

9:15 **Gastrointestinal and Nutritional Aspects of Alcoholism**
Frank L. Iber, MD, Baltimore

10:00 **Rational Drug Therapy for Alcoholism (including withdrawal methods and use of Disulfiram)**
Charles E. Becker, MD, San Francisco

10:40 Coffee Break

11:00 **Question and Answer Period**

Moderator: Arthur Bolter, MD, San Leandro

11:15 **The Pharmacology of the Drugs of Abuse**
Robert Roe, MD, San Francisco

11:50 **Use of the Sedative-Hypnotics and Tranquilizers in Clinical Practice**
Leo Hollister, MD, Stanford

12:30 **Question and Answer Period**

12:45 Luncheon

1:30 **Alcoholism as a Socio-Political Issue**
Speakers to be announced

2:30 **Public Policies on Alcoholism and Other Drug Dependence**

Moderator: Stanford B. Rossiter, MD, Redwood City

Members of the Panel

Hon. Dianne Feinstein, Board of Supervisors, San Francisco
Hon. Arlen F. Gregorio, State Senator, District 12, San Mateo
Hon. Alan Sieroty, Assemblyman, District 59, Beverly Hills

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3:30 Break

3:45 **First Annual Meeting of the California Society for the Treatment of Alcoholism and Other Drug Dependencies**

MONDAY, MARCH 4 **Walnut Room**

Can Clergymen Share in Patient Care? We Need Each Other

The Role of the Clergyman in the 1974 Hospital

Chairman: A. Norton Donaldson, MD, Santa Ana

Sponsored by
CMA Committee on Medicine and Religion

9:30 **Can Clergymen Share in Patient Care? A Clergyman's View**
Monsignor Timothy E. O'Brien, San Francisco

10:00 **Can Clergymen Share in Patient Care? A Physician's View**
Malcolm S. M. Watts, MD, San Francisco

10:30 **Panel Discussion and Audience Dialogue**

Members of the Panel

George P. Carter, RB, STB, San Francisco
Dorothy B. Nielson, BS, RN, San Francisco
Monsignor Timothy O'Brien, San Francisco
Edward V. Stein, BD, PhD, San Anselmo
Malcolm S. M. Watts, MD, San Francisco

MONDAY, MARCH 4 **Rosewood Room**

Clinical Pharmacology for the Practitioner

Chairman: Henry W. Elliott, MD, Orange

Sponsored by
CMA Committee on Pharmacy and Therapeutics

Cosponsored by
University of California, Irvine, California College of Medicine

9:00 **Drug Interactions**
Howard Morrelli, MD, San Francisco

9:30 **Therapeutic Mishaps**
Frederick Meyers, MD, San Francisco

10:30 **Antibiotics**
E. Jack Benner, MD, Sacramento

11:10 **The Effects of Commonly Prescribed Drugs on Anesthesia**
Henry W. Elliott, MD, Orange

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MONDAY, MARCH 4 **Parlors 1, 2**

Government in Medicine Control or Cooperation

Cosponsored by
CMA Committee on Federal Legislation
California Medical Political Action Committee (CALPAC)

10:00 **The conference will deal with the major health-related legislative issues before the Congress in 1974.**

12:00 **Adjournment**

Scientific Section Meetings

ALLERGY

J. Garland Stroup, MD, Sacramento .... *Chairman*
Julian L. Harwell, MD, Pasadena .... *Secretary*
William J. Sayer, MD, Palo Alto .... *Assistant Secretary*

SUNDAY, MARCH 3 **Walnut Suite**

Diagnosis and Prophylaxis of Allergic Disease

Cosponsored by
California Society of Allergy and Clinical Immunology

8:50 **Introductory Remarks**
J. Garland Stroup, MD, Sacramento

9:00 **The Role of Lymphocytes in Atopic Disease**
Stanley Galant, MD, Irvine

9:20 **Allergy of the Nervous System**
Frederic Speer, MD, Shawnee Mission, Kansas

9:45 **Question and Answer Period**

10:00 Break

10:15 **Panel on Rast** (Radioallergosorbent test)
Zack Haddad, MD, Los Angeles
Douglas C. Heiner, MD, Torrance

10:50 **Question and Answer Period**

11:00 **The Prophylaxis of Allergic Disease**
Jerome Glaser, MD, Rochester, New York

11:45 **Question and Answer Period**

12:00 **Luncheon and Business Meeting** with the California Society of Allergy and Clinical Immunology

Reservation Fee $10
Please use reservation form on Page 24

2:00 **Management of Food Allergy in Adolescents and Adults**
Frederic Speer, MD, Shawnee Mission, Kansas

2:25 **The Beta Blockade Hypothesis—Some Additional Speculation**
Gildon N. Beall, MD, Torrance

2:45 **Question and Answer Period**
Reports from Allergy Trainees

3:00 **Binding of Catecholamine by Lymphocytes**
William Sokal, MD, Torrance

3:15 **Immunoglobulin in Amniotic Fluid and Cord Blood**
Allan Singer, MD, Torrance

3:30 **IGE Levels in the Patient with Cancer**
Richard Roth, MD, Torrance

3:45 **Status of Delayed Hypersensitivity in the Atopic Patient**
Richard Davis, MD, Irvine

4:00 **The Use of PHA Skin Test as a Tool for Delayed Hypersensitivity**
Michael Franz, MD, Irvine

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ANESTHESIOLOGY

John C. Damron, MD, Palo Alto .... *Chairman*
Edwin H. Lewis, MD, San Diego .... *Secretary*
Lynn W. Winchester, MD, Palo Alto .... *Assistant Secretary*

SUNDAY, MARCH 3 **Ballroom 6**

Pulmonary Problems Before, During and After Surgery

Moderator: Wilbur Y. Hallett, MD, Burbank

JOINT MEETING
Section on Anesthesiology
Section on Chest Diseases

Cosponsored by
California Chapter, American College of Chest Physicians
California Society of Anesthesiologists
California Thoracic Society

8:15 **Anesthesiology Section Business Meeting**

8:45 **Registration**

9:00 INTRODUCTION: **Respiratory Cost of Surgery**
Wilbur Y. Hallett, MD, Burbank

PANEL: **Preoperative Preparation**
Moderator: E. A. Gaensler, MD, Boston

9:10 **The Pulmonary Patient and Non-Thoracic Surgery**
Frederick Glauser, MD, San Jose

9:30 **Thoracic Surgery—"Resectability"**
John E. Hodgkin, MD, Loma Linda

9:50 **Preparation of the Pulmonary Patient for Surgery**
Irwin Ziment, MD, Los Angeles

10:10 Coffee Break

10:25 **Selecting Anesthesia for the Pulmonary Patient**
John Eisele, MD, Davis

10:40 **Discussion**

11:20 **Lung Injury after Surgery**
Norman C. Staub, MD, San Francisco

12:00 Luncheon Break

12:30 Luncheon (advance registrants only)

Pulmonary Physiologist vs. Thoracic Surgeon
E. A. Gaensler, MD, Boston

Reservation Fee $10
Please use reservation form on Page 24

PANEL: **Recognition, Prevention and Treatment c Specific Complications**
Moderator: Kenneth M. Moser, MD, San Diego

2:00 **Atelectasis, O_2 Toxicity**
Morley Singer, MD, San Francisco

2:20 **Thrombo-Embolic Events and Cardiac Failure**
Myron Stein, MD, Los Angeles

2:40 **Shock Lung and the Adult Respiratory Distress Syndrome**
Carroll Cross, MD, Davis

3:00 **Discussion**

3:25 Break

PANEL: **Postoperative Respiratory Failure**
Moderator: H. Barrie Fairley, MB, BS, San Francisco

3:40 **Introduction**
H. Barrie Fairley, MB, BS, San Francisco

3:55 **Oxygenation and Acid Base Balance, Maintaining and Measuring, Newer Techniques**
Philip M. Gold, MD, San Bernardino

4:15 **Implications of the Work of Breathing in the Postoperative Patient**
Richard Peters, MD, San Mateo

4:35 **Discussion and Wrap-up**
Panel and Moderator
E. A. Gaensler, MD, Boston

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CHEST DISEASES

Angelo May, MD, San Francisco	*Chairman*
Robert B. Stone, MD, Oakland	*Secretary*
Wilbur Y. Hallett, MD, Burbank	*Assistant Secretary*

SUNDAY, MARCH 3 **Ballroom 6**

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Section on Chest Diseases

Cosponsored by
California Chapter, American College of Chest Physicians
California Society of Anesthesiologists
California Thoracic Society

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E. A. Gaensler, MD, Boston

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5:00 **Chest Diseases Section Business Meeting**

Visit the
Scientific and Organizational Exhibits

Garden Lane, California Room
and
North Lounge

MARCH 2-5, 1974
9:00 a.m. to 5:00 p.m.

DERMATOLOGY

Richard Mihan, MD, Los Angeles	*Chairman*
Ellis N. Mitchell, MD, Greenbrae	*Secretary*
Marian M. Brubaker, MD, La Canada	*Assistant Secretary*

SUNDAY, MARCH 3 **Rosewood Suite**

Practical Therapeutics in Dermatology

Moderator: Richard Mihan, MD, Los Angeles

Cosponsored by
University of California, San Francisco, School of Medicine
San Francisco Dermatological Society

8:30 **Topical Corticosteroid Therapy: Its Use and Abuse**
Faye Arundell, MD, Menlo Park

8:50 **Psoriasis Day Care Center Therapy**
Eugene Farber, MD, Stanford
William Watson, MD, San Bruno

9:10 **Treatment of Common Virus and Parasitic Diseases of the Skin**
Marcus Conant, MD, San Francisco

9:35 **The Management of Acute and Chronic Urticaria**
William Akers, MD, San Francisco

9:55 **Question and Answer Period**

10:10 Coffee Break

10:25 **Dermatology Section Business Meeting**

10:40 **An Overview of Newer Treatment in Dermatology**
Rees B. Rees, MD, San Francisco

11:10 **Skin Cancer Therapy**
Theodore Tromovitch, MD, San Francisco

11:40 **Fungus Diseases of the Skin: A Practical Approach to Diagnosis and Therapy**
Paul Jacobs, MD, Palo Alto

12:00 **Question and Answer Period**

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GENERAL AND FAMILY PRACTICE

Peter J. Kistler, MD, San Bruno	*Chairman*
Holger Rasmussen, MD, Fremont	*Secretary*
Caesar O. Julian, MD, Simi Valley	*Assistant Secretary*

SATURDAY, MARCH 2 **Parlor 1, 2, 3**

Medicine's Untamed Frontier, The Emergency Room

Moderator: John Bridgeman, MD, Mission Viejo

Cosponsored by
California Chapter, American College of
Emergency Room Physicians
University of California, Davis, School of Medicine

TRAINING THE EMERGENCY ROOM PHYSICIAN

9:00 **Specialists in Emergency Medicine**
Gail V. Anderson, MD, Los Angeles

9:30 **Family Practice Fits the Bill**
William R. Nesbitt, MD, Davis

10:00 **Recruitment and Compensation**
Karl G. Mangold, MD, San Leandro

10:30 **The Community Hospital Viewpoint**
Mr. Mark Tanaka, Sacramento

11:00 **The Legal Viewpoint**
David E. Willett, Esq., San Francisco

11:30 **Roundtable Discussion**
Edward K. Blasdel, MD, Berkeley

12:00 **General and Family Practice Section Business Meetir**

Moderator: Stanley G. Gold, MD, Fullerton

1:30 **Anti-Arrhythymics in Suspected Myocardial Infarctic**
Milford G. Wyman, MD, Los Angeles

2:15 **The Patient with Multiple Injuries**
Robert C. Lim, Jr., MD, San Francisco

3:00 **Bites by Venomous "Critters"**
Findlay Russell, MD, San Diego

Acceptable for Category I Credit under
the CMA Certification Program

GENERAL SURGERY

Albert D. Hall, MD, San Francisco	*Chairm*
David B. Hinshaw, MD, Loma Linda	*Secreta*
Earl W. Wolfman, Jr., MD, Davis	*Assistant Secreta*

MONDAY, MARCH 4 **Ballroom**

Current Trends in Gastrointestinal Surge

Cosponsored by
American College of Surgeons
Northern and Southern California Chapters

Reservation Fee $10
Please use reservation form on Page 24

12:00 **Luncheon Meeting** Jointly with American College
Surgeons, Northern and Southern California Chapt
Moderator: Albert D. Hall, MD, San Francisco

12:45 **Luncheon Address**
Current Trends in the Surgical Management of Inflammatory Enterocolitis
Rupert B. Turnbull, Jr., MD, Cleveland, Ohio

1:30 **Panel Discussion:**
Current Trends in the Management of an Upper Gastrointestinal Problem Case
Moderator: Harry A. Oberhelman, Jr., MD, Palo Alt
Members of the Panel
Lawrence P. Bogle, MD, San Diego
Rupert B. Turnbull, Jr., MD, Cleveland, Ohio
David W. Watson, MD, Davis

2:15 **Question and Answer Period**

2:30 **Current Status of the Surgical Treatment of Mor Obesity**
Carl E. Schwab, MD, Laguna Beach

3:00 Break

3:15 **Current Status of the "No-Touch" Technique in Cancer Surgery**
Rupert B. Turnbull, Jr., MD, Cleveland, Ohio

3:45 **Panel Discussion:**
Current Trends in the Surgical Management of the Lower Gastrointestinal Problem Case
Moderator: Victor Richards, MD, San Francisco
Members of the Panel
Lawrence P. Bogle, MD, San Diego
Theodore R. Schrock, MD, San Francisco
Rupert B. Turnbull, Jr., MD, Cleveland, Ohio

4:30 **Question and Answer Period**

Acceptable for Category I Credit under the CMA Certification Program

4:45 **General Surgery Section Business Meeting**

INDUSTRIAL MEDICINE AND SURGERY

nthony A. Mira, MD, Santa Monica .... *Chairman*
ohn Meyers, MD, San Francisco .... *Secretary*
dward J. O'Neill, MD, Woodland Hills . *Assistant Secretary*

ONDAY, MARCH 4 **Parlor 3**

JOINT MEETING
Section on Industrial Medicine and Surgery
Section on Orthopedics
Section on Physical Medicine and Rehabilitation
Section on Psychiatry

Cosponsored by
Western Industrial Medical Association

3:00 **Welcome and Introductions**
John E. Meyers, MD, San Francisco

3:05 **Our Responsibility to the Injured Employee**
A State Legislator to be announced

3:30 **The Physician's Responsibility to the Disabled Worker**
Homer Pheasant, MD, Los Angeles

:00 **The Need for Early Rehabilitation from the Treating Physician**
L. J. Trijiano, MD, San Francisco

:30 **The Patient's Responsibility in His Own Rehabilitation**
Mr. Gregory Sells, Fresno

:15 Break

:30 **Management's Responsibility to the Injured Employee**
Mr. William Kugler, San Leandro

1:00 **Psychological Factors Involved in Rehabilitation**
Allen Enelow, MD, San Francisco

:45 Lunch Break

:30 **Industrial Medicine and Surgery Section Business Meeting**

:00 **The Need for Motivation in Rehabilitation**
49er Professional Football Player

1:30 **The Insurance Company's Responsibility to the Injured Employee**
Robert Hassard, Esq., San Francisco

2:00 **Legal View of Medical Rehabilitation**
Hon. Carlos Bee, Assemblyman, District 13, Hayward

2:30 Break

2:45 **The Orchestration of Rehabilitation**
Steven Levitt, MD, Berkeley

3:30 **Question and Answer Period**
Panel

Acceptable for Category I Credit under the CMA Certification Program

INTERNAL MEDICINE

Augustus F. Stiegler, MD, San Francisco .... *Chairman*
Edwin V. Banta, Jr., MD, Redlands .... *Secretary*
Daniel W. Black, MD, Castro Valley .... *Assistant Secretary*

Federated Meeting
American College of Physicians
CMA Section on Internal Medicine

Registration Fee $20
See registration form on Page 25

FRIDAY, MARCH 1 **Colonial Room St. Francis Hotel**

12:00 **Registration**

1:50 **Welcome**
Maurice Fox, MD, Palo Alto

RECENT DEVELOPMENTS IN MYOCARDIAL INFARCTION
Moderator: Howard F. Morrelli, MD, San Francisco

2:00 **Therapy of Cardiogenic Shock in Myocardial Infarction**
William Parmley, MD, Los Angeles

2:30 **Therapy of Arrhythmias in Myocardial Infarction**
Melvin Scheinman, MD, San Francisco

3:00 **Question and Answer Period**

3:10 Break

3:30
CURRENT DEVELOPMENTS IN DERMATOLOGIC DIAGNOSIS AND THERAPY
Moderator: Howard I. Maibach, MD, San Francisco

3:40 **Drug Induced Photosensitivity: A Common Problem**
John H. Epstein, MD, San Francisco

3:50 **An Emergency Life Threatening Dermatosis: Epidermal Necrolysis**
Ervin H. Epstein, Jr., MD, Oakland

4:00 **Psoriatic Nail Arthropathy**
Eugene M. Farber, MD, Palo Alto

4:10 **Medical Aspects of Lues: Gastric Crisis, Hepatitis and Nephrosis**
Marcus A. Conant, MD, San Francisco

4:20 **Cutaneous Hypo and Hyperpigmented Macules in Diagnosis of Systemic Disease**
David L. Cram, MD, San Francisco

4:30 **Vitamin E and Thee**
Rees B. Rees, Jr., MD, San Francisco

4:40 **Nuances in Diagnosis of Reactive Serologic Test for Syphilis**
Denny L. Tuffanelli, MD, San Francisco

4:50 **Fads and Fashions in Contact Dermatitis: 1974**
Howard I. Maibach, MD, San Francisco

5:00 Social Hour

SATURDAY, MARCH 2

THYROID DISEASE

Moderator: Francis S. Greenspan, MD, San Francisco

8:30 **Diagnostic Techniques in Thyrotoxicosis**
Sidney Ingbar, MD, San Francisco

9:00 **Newer Concepts in the Pathogenesis and Therapy of Grave's Ophthalmopathy**
Joseph P. Kriss, MD, Stanford

9:30 **Thyroid Nodules and Thyroid Cancer**
Francis S. Greenspan, MD, San Francisco

10:00 **Discussion**

10:15 Break

10:45 **Topic to be announced**

11:30 **Presentation by Official College Representative of the American College of Physicians**

12:00 **Luncheon** with Faculty from Stanford University, School of Medicine and University of California, School of Medicine, San Francisco

FATS AND SUGAR

Moderator: Lawrence V. Basso, MD, Palo Alto

1:30 **A Declassification of the Hyperlipidemias**
Gerald Reaven, MD, Stanford

1:55 **The Hypoglycemia Problem**
Maurice Fox, MD, Palo Alto

2:20 **Oral Hypoglycemic Agents, 1974**
Henry Bourne, MD, San Francisco

2:45 Break

HEMATOLOGIC PROBLEMS

Moderator: Robert A. O'Reilly, MD, San Jose

3:15 **Common Anemias Seen by Internists**
Ralph O. Wallerstein, MD, San Francisco

3:40 **Defects in Red Blood Cell Metabolism, Intracorpuscular Defects Resulting in Hemolysis**
Stanley Schrier, MD, Stanford

4:05 **Disseminated Intravascular Coagulation**
William P. Creger, MD, Palo Alto

4:30 **Question and Answer Period**

4:45 **Internal Medicine Section Business Meeting**

NEUROLOGY

Edward H. Davis, MD, Los Angeles .... *Chairm*
Edward E. Shev, MD, San Francisco .... *Secreta*
James R. Nelson, MD, La Jolla .... *Assistant Secreta*

Electromyography as an Aid in Neurologic Diagnosis

JOINT MEETING
Section on Neurology
Section on Orthopedics
Section on Physical Medicine and Rehabilitation

Cosponsored by
American Academy of Physical Medicine and Rehabilitati
St. Mary's Hospital and Medical Center, San Francisco

THURSDAY, FEBRUARY 28

Morrissey Auditorium
St. Mary's Hospital and Medical Center
Hayes and Stanyan Streets, San Francisco

8:30 **Preregistration** for CMA Annual Session

9:00 **Program to Be Announced**

FRIDAY, MARCH 1

Morrissey Auditorium
St. Mary's Hospital and Medical Center
Hayes and Stanyan Streets, San Francisco

9:00 **Program to Be Announced**

SATURDAY, MARCH 2

Fireman's Fund American Insurance Company Auditorium
3333 California Street, San Francisco

Moderator: W. Harvey Moore, MD, San Leandro

9:00 **The Widening Clinical Applications of Electromyography**
M. Michael Gassel, MD, San Francisco

9:45 **Neck and Arm Pain: An Electronic Odyssey**
Walter J. Treanor, MD, San Francisco

10:10 **Research in Acute Entrapment Syndromes**
Roger W. Gilliatt, MD, London

10:45 Break

11:00 **Proximal Neuropathies: Panel Discussion:**
Root Avulsions
Brachial Plexitis
Femoral-Sciatic Neuropathies
Members of the Panel
George H. Kraft, MD, Seattle, Washington
M. Michael Gassell, MD, San Francisco
Arthur K. Asbury, MD, San Francisco

11:45 **Thoracic Outlet Syndromes—A Critique**
Roger W. Gilliatt, MD, London

12:15 **Question and Answer Period**

2:30 Luncheon

Moderator: Edward E. Shev, MD, San Francisco

2:00 **Electromyography in Lumbar Radiculopathy Diagnostic Advantages and Abuses**
George H. Kraft, MD, Seattle, Washington

2:45 **The Electromyogram in Prognosis: A Panel**
Bell's Palsy
Recovering Nerve Injury
Saturday Night Palsies
Denervation in Upper Motor Neuron Disease
Members of the Panel
Roger W. Gilliatt, MD, London
Austin J. Sumner, MD, San Francisco
Robert G. Taylor, MD, Davis

4:00 **Towards Standards and Qualifications in Clinical Electromyography**
W. C. Wiederholt, MD, San Diego

4:30 **Question and Answer Period**

Acceptable for Category I Credit under the CMA Certification Program

UNDAY, MARCH 3 Rosewood Suite

Cosponsored by
niversity of California, San Francisco, School of Medicine

1:30 **Physical Causes of Headaches**
Pierre Dreyfus, MD, Davis

2:15 **Migraine and Associated Problems**
E. Davis, MD, San Francisco

3:00 **Headaches of Psychosomatic Origin**
Edward E. Shev, MD, San Francisco

3:30 **Discussion**

Acceptable for Category I Credit under the CMA Certification Program

4:00 **Section on Neurology Business Meeting**

OBSTETRICS AND GYNECOLOGY

illiam F. Kroener, Jr., MD, Whittier	*Chairman*
harles E. Weber, MD, La Jolla	*Secretary*
heodore W. Loring, MD, Eureka	*Assistant Secretary*

ONDAY, MARCH 4 Ballroom 5

High Risk Pregnancy

Cosponsored by
California Section of District 8 American College of Obstetrics and Gynecology

8:45 **Welcome**
William F. Kroener, MD, Whittier

9:00 **Identification and Prediction of the High Risk Pregnancy and Neonate**
Calvin Hobel, MD, Torrance

9:45 **Management of High Risk Pregnancy and Fetal Monitoring**
John Queenan, MD, Louisville, Kentucky

0:30 Break

11:00 **Ob-Gyn Emergencies**
Gail Anderson, MD, Los Angeles

12:15 **Luncheon**
Presiding: Lester T. Hibbard, MD, Los Angeles

Reservation Fee $10
Please use reservation form on Page 24

ONCOLOGY

1:00 **Current Experience in Management of Ovarian and Endometrial Cancer**
Julian Smith, MD, Houston, Texas

2:00 Break

2:15 **Section on Obstetrics and Gynecology Business Meeting**

2:30 **The Challenge of Sex Transformation (Evaluation and Results)**
Richard Green, MD, Los Angeles

Acceptable for Category I Credit under the CMA Certification Program

OPHTHALMOLOGY

John A. Berg, MD, Sacramento	*Chairman*
Robert E. Christensen, MD, Los Angeles	*Secretary*
Jerry F. Donin, MD, Pomona	*Assistant Secretary*

SATURDAY, MARCH 2 Ballroom 4

Malpractice in Ophthalmology

Cosponsored by
California Association of Ophthalmologists
Pacific Medical Center

Reservation Fee: $10
Please use reservation form on Page 25

10:00 **Registration**

10:30 **Introduction**
John A. Berg, MD, Sacramento

Report of the President of the California Association of Ophthalmologists
Theodore Steinberg, MD, Fresno

Current Trends in Ophthalmology
Executive Members of the CAO Board

12:00 Luncheon
Guest Speaker: J. M. Stubblebine, MD, Sacramento

1:30 **Informed Consent**
Jerome W. Bettman, MD, Woodside

1:45 **Malpractice Trends**
David S. Rubsamen, MD, LLD, Berkeley

2:15 **Malpractice Defense**
Salvatore Bossio, Esq., San Francisco

2:45 **Question and Answer Period**

3:00 **Adjournment**

SUNDAY, MARCH 3 Ballroom 5

Neuro-Ophthalmology Symposium

Cosponsored by
Pacific Medical Center, San Francisco

The Anterior Visual Pathways

Moderator: Robert E. Christensen, MD, Los Angeles

9:00 **Introduction**
John A. Berg, MD, Sacramento

9:10 **The Visible Signs of Anterior Visual Pathway Lesions Fundoscopy of the Nerve Fiber Layer**
William F. Hoyt, MD, San Francisco
Nancy Newman, MD, San Francisco

9:50 **Nerve Fiber Bundle Field Defects Detection of Early Defects**
David O. Harrington, MD, San Francisco

10:10 Break

10:30 **Fluorescein Angiography—Help or Hindrance**
John C. Cavender, MD, San Francisco

10:55 **Interesting Optic Papillopathies**
David L. Knox, MD, Baltimore, Maryland

Acceptable for Category I Credit under the CMA Certification Program

11:25 **Question and Answer Period**

11:45 **Section on Ophthalmology Business Meeting**

12:00 Luncheon

Sellar and Parasellar Lesions

Moderator: Nancy Newman, MD, San Francisco

1:15 **Why to Suspect a Chiasmal Lesion**
Robert S. Hepler, MD, Los Angeles

1:35 **Expected and Unexpected Field Defects in Sellar and Parasellar Lesions**
David O. Harrington, MD, San Francisco

1:50 **Chiasmal Problems in Private Practice**
Jerry F. Donin, MD, Pomona

2:05 **Visual Aberrations with Sellar Lesions**
Nancy Newman, MD, San Francisco

2:20 **Pathologic Anatomy and Clinical Indications for Neurosurgical Referral**
William F. Hoyt, MD, San Francisco
Charles B. Wilson, MD, San Francisco

3:00 Break

3:15 **"Optic Neuritis"—Misdiagnoses**
David L. Knox, MD, Baltimore, Maryland

3:45 **Question and Answer Period**

Acceptable for Category I Credit under the CMA Certification Program

ORTHOPEDICS

Michael Shlens, MD, Los Angeles .... *Chairma*
Thomas H. Christianson, MD, Carmichael .... *Secreta*
Steven A. Pye, Jr., MD, San Diego .... *Assistant Secreta*

Electromyography as an Aid in Neurologic Diagnosis

JOINT MEETING
Section on Neurology
Section on Orthopedics
Section on Physical Medicine and Rehabilitation

Cosponsored by
American Academy of Physical Medicine and Rehabilitati
St. Mary's Hospital and Medical Center, San Francisco

THURSDAY, FEBRUARY 28

Morrissey Auditorium
St. Mary's Hospital and Medical Center
Hayes and Stanyan Streets, San Francisco

8:30 **Preregistration** for CMA Annual Session

9:00 **Program to Be Announced**

FRIDAY, MARCH 1

Morrissey Auditorium
St. Mary's Hospital and Medical Center
Hayes and Stanyan Streets, San Francisco

9:00 **Program to Be Announced**

SATURDAY, MARCH 2

Fireman's Fund American Insurance Company Auditorium
3333 California Street, San Francisco

Moderator: W. Harvey Moore, MD, San Leandro

9:00 **The Widening Clinical Applications of Electromyography**
M. Michael Gassel, MD, San Francisco

9:45 **Neck and Arm Pain: An Electronic Odyssey**
Walter J. Treanor, MD, San Francisco

10:10 **Research in Acute Entrapment Syndromes**
Roger W. Gilliatt, MD, London

10:45 Break
Section on Orthopedics Business Meeting

11:00 **Proximal Neuropathies: Panel Discussion:**
Root Avulsions
Brachial Plexitis
Femoral-Sciatic Neuropathies

Members of the Panel
George H. Kraft, MD, Seattle, Washington
M. Michael Gassell, MD, San Francisco
Arthur K. Asbury, MD, San Francisco

11:45 **Thoracic Outlet Syndromes—A Critique**
Roger W. Gilliatt, MD, London

12:15 **Question and Answer Period**

2:30 Luncheon

Moderator: Edward E. Shev, MD, San Francisco

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George H. Kraft, MD, Seattle, Washington

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Recovering Nerve Injury
Saturday Night Palsies
Denervation in Upper Motor Neuron Disease
Members of the Panel
Roger W. Gilliatt, MD, London
Austin J. Sumner, MD, San Francisco
Robert G. Taylor, MD, Davis

4:00 **Towards Standards and Qualifications in Clinical Electromyography**
W. C. Wiederholt, MD, San Diego

4:30 **Question and Answer Period**

Acceptable for Category I Credit under the CMA Certification Program

IONDAY, MARCH 4 Parlor 3

JOINT MEETING
Section on Industrial Medicine and Surgery
Section on Orthopedics
Section on Physical Medicine and Rehabilitation
Section on Psychiatry

Cosponsored by
Western Industrial Medical Association

8:00 **Welcome and Introductions**
John E. Meyers, MD, San Francisco

8:05 **Our Responsibility to the Injured Employee**
A State Legislator to be announced

8:30 **The Physician's Responsibility to the Disabled Worker**
Homer Pheasant, MD, Los Angeles

9:00 **The Need for Early Rehabilitation from the Treating Physician**
L. J. Trijiano, MD, San Francisco

9:30 **The Patient's Responsibility in His Own Rehabilitation**
Mr. Gregory Sells, Fresno

0:15 Break

0:30 **Management's Responsibility to the Injured Employee**
Mr. William Kugler, San Leandro

1:00 **Psychological Factors Involved in Rehabilitation**
Allen Enelow, MD, San Francisco

1:45 Lunch Break

1:00 **The Need for Motivation in Rehabilitation**
49er Professional Football Player

1:30 **The Insurance Company's Responsibility to the Injured Employee**
Robert Hassard, Esq., San Francisco

2:00 **Legal View of Medical Rehabilitation**
Hon. Carlos Bee, Assemblyman, District 13, Hayward

2:30 Break

2:45 **The Orchestration of Rehabilitation**
Steven Levitt, MD, Berkeley

3:30 **Question and Answer Period**
Panel

Acceptable for Category I Credit under the CMA Certification Program

OTOLARYNGOLOGY

Richard Goode, MD, Stanford .... *Chairman*
William Simpson, MD, Los Angeles .... *Secretary*
Mansfield F. W. Smith, MD, Stanford ... *Assistant Secretary*

SUNDAY, MARCH 3 Teakwood Suite

Conservation of Hearing in Noise

Cosponsored by
CMA Committee on Environmental Health
Stanford University School of Medicine

9:00 **The Noise Problem—An Overview**
Joseph Sataloff, MD, Philadelphia, Pennsylvania

9:45 **Dynamics of Hearing, Hearing Measurement, Pathophysiology of Cochlear Injury by Noise**
Theodore J. Glattke, PhD, Stanford

10:30 **Discussion**
Coffee Break

11:00 **The Law and Noise**
Federal Noise Standards and Occupational Safety and Health Act
State of California
Workmen's Compensation
Definition of Harmful Noise
Damage Risk Criteria
J. Howard Bunn, Jr., Esq., Raleigh, North Carolina

11:45 **Discussion**

12:00 Luncheon

1:00 **Section on Otolaryngology Business Meeting**

1:15 **Practical Problems in Hearing Conservation**
Joseph Sataloff, MD, Philadelphia, Pennsylvania

2:00 **Discussion**

2:15 **Noise Measurement**
Mr. Dan Adair, Portland, Oregon

2:45 **Non-occupational Noise Hazards**
Charles Lebo, MD, Stanford

3:15 **Non-auditory Effects of Noise**
Maurice Schiff, MD, La Jolla

3:45 **Role of the Physician in the Prevention, Diagnosis and Management of Noise Induced Hearing Loss**
John B. Shinn, MD, Stanford

4:15 **Discussion**

Acceptable for Category I Credit under the CMA Certification Program

PATHOLOGY

David Korn, MD, Stanford	*Chairman*
Phillips Gausewitz, MD, San Diego	*Secretary*
Stebbins Chandor, MD, Los Angeles	*Assistant Secretary*

SATURDAY, MARCH 2 **Parlors 7, 8, 9**

Advances in Laboratory Diagnosis of Genetic Disorders and Clinical Application

JOINT MEETING
Section on Pathology
Section on Pediatrics

Cosponsored by
American Academy of Pediatrics, Chapter I
California Society of Pathologists

9:00 **Prenatal Diagnosis of Genetic Defects**
Mitchell S. Golbus, MD, San Francisco

9:30 **Differential Diagnosis of Abnormal Sexual Development**
Daniel D. Federman, MD, Stanford

10:00 **Recent Advances in Cytogenetics**
Felix Conte, MD, San Francisco

10:30 Break

10:30 **Section on Pathology Business Meeting**

10:45 **Prenatal Diagnosis of Metabolic Disorders**
John S. O'Brien, MD, La Jolla

11:15 **Panel Discussion:** Illustrative Case Discussion and Question and Answer Period
Moderator: Frederick Frye, MD, San Diego
Members of the Panel
Mitchell S. Golbus, MD, San Francisco
Daniel D. Federman, MD, Stanford
Felix Conte, MD, San Francisco
John S. O'Brien, MD, La Jolla

Acceptable for Category I Credit under
the CMA Certification Program

PEDIATRICS

Frederick Frye, MD, San Diego	*Chairman*
Leon P. Smith, MD, Mill Valley	*Secretary*
Nord Nation, MD, Los Angeles	*Assistant Secretary*

SATURDAY, MARCH 2 **Parlors 7, 8, 9**

Advances in Laboratory Diagnosis of Genetic Disorders and Clinical Application

JOINT MEETING
Section on Pathology
Section on Pediatrics

Cosponsored by
American Academy of Pediatrics, Chapter I
California Society of Pathologists

8:45 **Section on Pediatrics Business Meeting**

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Felix Conte, MD, San Francisco
John S. O'Brien, MD, La Jolla

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the CMA Certification Program

PHYSICAL MEDICINE AND REHABILITATION

W. Harvey Moore, MD, San Leandro	*Chairma*
Seth H. Douthett, MD, Long Beach	*Secreta*
Walter J. Treanor, MD, San Francisco	*Assistant Secreta*

Electromyography as an Aid in Neurologic Diagnosis

JOINT MEETING
Section on Physical Medicine and Rehabilitation
Section on Neurology
Section on Orthopedics

Cosponsored by
American Academy of Physical Medicine and Rehabilitati
St. Mary's Hospital and Medical Center, San Francisco

THURSDAY, FEBRUARY 28

Morrissey Auditorium
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Hayes and Stanyan Streets, San Francisco

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Auditorium
3333 California Street, San Francisco

Moderator: W. Harvey Moore, MD, San Leandro

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M. Michael Gassel, MD, San Francisco

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Brachial Plexitis
Femoral-Sciatic Neuropathies
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M. Michael Gassell, MD, San Francisco
Arthur K. Asbury, MD, San Francisco

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Roger W. Gilliatt, MD, London

12:15 **Question and Answer Period**

Acceptable for Category I Credit under the CMA Certification Program

12:30 **Section on Physical Medicine and Rehabilitation Business Meeting**

Luncheon

Moderator: Edward E. Shev, MD, San Francisco

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George H. Kraft, MD, Seattle, Washington

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Robert G. Taylor, MD, Davis

4:00 **Towards Standards and Qualifications in Clinical Electromyography**
W. C. Wiederholt, MD, San Diego

4:30 **Question and Answer Period**

Acceptable for Category I Credit under the CMA Certification Program

MONDAY, MARCH 4 Parlor 3

JOINT MEETING
Section on Industrial Medicine and Surgery
Section on Orthopedics
Section on Physical Medicine and Rehabilitation
Section on Psychiatry

Cosponsored by
Western Industrial Medical Association

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2:45 **The Orchestration of Rehabilitation**
Steven Levitt, MD, Berkeley

3:30 **Question and Answer Period**
Panel

Acceptable for Category I Credit under the CMA Certification Program

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Visit the Technical Exhibits

Imperial Ballroom
and
Franciscan Room

MARCH 2-5, 1974
9:00 a.m. to 5:00 p.m.

PLASTIC SURGERY

E. C. Brown, MD, San Francisco .... *Chairman*
Roger P. Friedenthal, MD, San Francisco .... *Secretary*
Frederick M. Grazer, MD, Newport Beach *Assistant Secretary*

MONDAY, MARCH 4 **Parlor 9**

Advances in Plastic Surgery Applicable to General Medicine and Surgery

Cosponsored by
California Society of Plastic Surgeons
University of California, School of Medicine, San Francisco

Special Conference: Enrollment limited to 40 physicians

10:00 **Principles of Plastic Surgical Wound Closure, with Laboratory**
William Morris, MD, San Francisco

12:00 Luncheon Break

BURNS

1:30 **Acute and Emergency Measures**
Lawrence Foster, Jr., MD, San Francisco

2:00 **Advances in Local Treatment**
Gary Friedman, MD, San Francisco

2:30 **Keloids and Their Treatment**
Stephen Miller, MD, San Francisco

3:00 Break

3:15 **Plastic Surgery Section Business Meeting**

RECONSTRUCTIVE SURGERY OF THE BREAST

3:30 **Augmentation Mammoplasty**
Roger Greenberg, MD, San Francisco

4:00 **Reduction Mammoplasty**
Angelo Capozzi, MD, San Francisco

4:30 **Subcutaneous Mastectomy with Implants for Benign Breast Disease**
Vincent R. Pennisi, MD, San Francisco

5:00 **Question and Answer Period**

Acceptable for Category I Credit under
the CMA Certification Program

Visit the
Scientific and Organizational Exhibits

Garden Lane, California Room
and
North Lounge

MARCH 2-5, 1974
9:00 a.m. to 5:00 p.m.

PREVENTIVE MEDICINE AND PUBLIC HEALTH

Donald G. Ramras, MD, San Diego .... *Chairma*
Colin T. Greenlaw, MD, Sacramento .... *Secretar*
Allyn G. Bridge, MD, Riverside .... *Assistant Secretar*

MONDAY, MARCH 4 **Ballroom**

The World of Viruses Pathogenic for Man World Travelers

Moderator: Colin T. Greenlaw, MD, Sacramento

Cosponsored by
University of California, Davis, School of Medicine
Loma Linda University, School of Health, Loma Linda

8:15 **Influenza Viruses—Which Variant Will Strike Next, and Where?**
Stephan Billstein, MD, MPH, Sacramento

9:00 **Viral Hepatitis**
Saul Krugman, MD, New York City

9:50 Coffee Break

10:00 **Viral Diseases Transmissable from Animals to Ma**
George Humphrey, DVM, MPH, Berkeley
Victor J. Cabasso, MS, ScD, Berkeley

11:40 **Section Business Meeting**

1:15 **Immunizations Against Viral Diseases**
Moderator: Donald G. Ramras, MD, *San Diego*
Members of the Panel
Stephan Billstein, MD, MPH, Sacramento
Victor J. Cabasso, MS, ScD, Berkeley
Paul Hoeprich, MD, Davis
George Humphrey, DVM, MPH, Berkeley
Saul Krugman, MD, New York City

2:00 **Viral Encephalitis and Meningitis**
Paul Hoeprich, MD, Davis

2:45 Break

2:55 **Importable Diseases**
Myron G. Schultz, DVM, MD, Atlanta, Georgia

3:50 **Viral Colorado Tick Fever Versus Rocky Mounta Spotted Fever**
Richard W. Emmons, MD, DTM & H, MPH, PhD, Berkeley

Acceptable for Category I Credit under
the CMA Certification Program

PSYCHIATRY

John S. Peck, MD, Encino .... *Chairman*
Harvey C. Small, MD, San Mateo .... *Secretary*
George Gross, MD, Sacramento ...... *Assistant Secretary*

SUNDAY, MARCH 3 — Parlor 3

Cosponsored by
Central Valley Psychiatric Society
Northern California Psychiatric Society

VIOLENCE AND MEDICAL PRACTICE

Moderator: Joe P. Tupin, MD, Davis

9:00 **Causes of Violence**
John Adams, MD, Stanford

9:30 **Alternatives to Violence**
Frederic W. Ilfeld, MD, Davis

10:00 Break

10:15 **Understanding the Psychodynamics of the Murderer**
George Solomon, MD, Fresno

11:00 **Question and Answer Period**

11:30 **Psychiatry Section Business Meeting**

12:00 Luncheon Break

HELPING CHILDREN AND THEIR FAMILIES

Moderator: Harvey C. Small, MD, San Mateo

1:00 **Current Views on Children and Divorce**
Noel H. Morrell, MD, Belmont

1:40 **Helping Parents at an Adolescent Center**
Murray Bilmes, PhD, Burlingame

3:15 Break

3:30 **Mental Health Consultation in the Pediatrician's Office**
Henry Richenbach, MD, Burlingame
Samuel Leavitt, MD, Burlingame
Martha Donner, MSW, San Mateo

4:15 **Question and Answer Period**

Acceptable for Category I Credit under
the CMA Certification Program

MONDAY, MARCH 4 — Parlor 3

JOINT MEETING

Section on Industrial Medicine and Surgery
Section on Orthopedics
Section on Physical Medicine and Rehabilitation
Section on Psychiatry

Cosponsored by
Western Industrial Medical Association

8:00 **Welcome and Introductions**
John E. Meyers, MD, San Francisco

8:05 **Our Responsibility to the Injured Employee**
A State Legislator to be announced

8:30 **The Physician's Responsibility to the Disabled Worker**
Homer Pheasant, MD, Los Angeles

9:00 **The Need for Early Rehabilitation from the Treating Physician**
L. J. Trijiano, MD, San Francisco

9:30 **The Patient's Responsibility in His Own Rehabilitation**
Mr. Gregory Sells, Fresno

10:15 Break

10:30 **Management's Responsibility to the Injured Employee**
Mr. William Kugler, San Leandro

11:00 **Psychological Factors Involved in Rehabilitation**
Allen Enelow, MD, San Francisco

11:45 Lunch Break

1:00 **The Need for Motivation in Rehabilitation**
49er Professional Football Player

1:30 **The Insurance Company's Responsibility to the Injured Employee**
Robert Hassard, Esq., San Francisco

2:00 **Legal View of Medical Rehabilitation**
Hon. Carlos Bee, Assemblyman, District 13, Hayward

2:30 Break

2:45 **The Orchestration of Rehabilitation**
Steven Levitt, MD, Berkeley

3:30 **Question and Answer Period**
Panel

Acceptable for Category I Credit under
the CMA Certification Program

RADIOLOGY

Robert H. Reid, MD, Los Gatos .... *Chairman*
Duane E. Blickenstaff, MD, La Jolla .... *Secretary*
Fred K. Sondheimer, MD, San Francisco *Assistant Secretary*

SUNDAY, MARCH 3 — Parlor 1, 2

Ultrasound In Medicine

Cosponsored by
University of Southern California, School of Medicine

8:30 **Radiology Section Business Meeting**

9:00 **The Use of Ultrasound in Urological Radiology**
Robert L. Wilson, MD, Los Angeles

9:35 **Ultrasound in Obstetrics and Gynecology**
Louis Bartolucci, MD, San Francisco

10:15 **The Three W's of Doppler Ultrasound in Medicine: What, When and Why**
Ross E. Brown, MD, Oklahoma City, Oklahoma

10:35 Break

10:50 **Diagnostic Ultrasound of the Liver, Pancreas, Gallbladder and Abdominal Aorta**
Granville C. Coggs, MD, San Francisco

11:20 **Cardiological Ultrasound**
Robert Kraus, MD, Los Angeles

11:50 **Question and Answer Period**

Acceptable for Category I Credit under
the CMA Certification Program

UROLOGY

Patrick H. McLin, MD, San Rafael .... *Chairman*
James G. Rohn, MD, Visalia .... *Secretary*
Eugene V. Cattolica, MD, Oakland ..... *Assistant Secretary*

MONDAY, MARCH 4 **Parlor 8**

Common Urological Problems

Cosponsored by
American Urological Association, Western Section

9:00 **Prostatitis—Bacterial and Nonbacterial**
William E. Fair, MD, Palo Alto

9:35 **Combined Urgency and Stress Incontinence**
Emil A. Tanagho, MD, San Francisco

10:15 Coffee Break

10:30 **Medical Legal Problems in Urology**—Panel Discussio
Moderator: David Rubsamen, MD, Berkeley
Members of the Panel
Marrs Craddick, Esq., Walnut Creek
H. Anthony Engelbrecht, MD, Oakland
Ruben Gittes, MD, San Diego
John Norton, MD, Berkeley

12:00 Lunch Break

1:15 **Section on Urology Business Meeting**

1:45 **Management of Urinary Calculi** (with notes on th use of the Nephroscope)
Ruben Gittes, MD, San Diego

2:45 **What to Do for Male Infertility?**
Moderator: Frank Hinman, MD, San Francisco
Members of the Panel
Sumner Marshall, MD, Berkeley
Stanwood Schmidt, MD, Eureka
Richard Weinstein, MD, Oakland

3:30 Coffee Break

3:45 **Dermatological Problems in Urology**
Ellis N. Mitchell, MD, Greenbrae

Acceptable for Category I Credit under the CMA Certification Program

Scientific and Organizational Exhibits

Note: Exhibit space has not yet been allocated. The following list of applicants for space in the Scientific and Organizational exhibit area is subject to approval by the Committee on Scientific Assemblies. A revised listing and description of the exhibits will be included in the hand program.

The Artificial Lens—Henry Hirschman, MD, Long Beach. Color photos will illustrate the evolution of lenses from inception to present. Models of the lenses and a carousel continuous projector will illustrate cases. A short summary of the exhibit will be distributed.

California Medical Association Certification and Accreditation of Continuing Medical Education Programs—Gabriel Sheridan and Richard Manley, San Francisco. The Committee on Continuing Medical Education and CMA staff will answer questions, distribute certification reporting forms and assist physicians with forms. An electronic demonstration of the Continuing Medical Education Program's storage and retrieval system will be given. Information on the CMA Accreditation of Continuing Medical Education Program for community hospitals and on the Consolidated Hospital Survey Program (JCAH-CMA) will also be available. Your comments and suggestions for California's future role in continuing medical education will be welcomed.

California Medical Association Physician Placement Service—Penny HildeBrandt, the coordinator of the Placement Service, will be on hand throughout the meeting to discuss opportunities for practice in California, and to take listings for the Placement Bulletin.

Common Dermatoses Seen in Office Practice—Harry Roth MD, San Francisco. This exhibit advises the general physician on psoriasis, atopic dermatitis and contact dermatitis. Also described as lichen planus, eczematous dermatitis and seborrhea. Visual comparison, to avoid confusion of dermatoses with other skin lesions is provided.

Computer Programs for Drug Dosage Regimens—Roger W Jelliffe, MD, Los Angeles. Computer programs develo dosage regimens of digitalis glycosides, pronestyl, xylocaine, kanamycin, gentamicin, and streptomycin, adjuste to weight, renal function, route of administration, serum potassium, and past dosage, to achieve selected bod concentrations or serum levels with reasonable accurac for most patients. The computer can be made accessibl to run by community hospitals over ordinary telephon lines.

Craniosynostosis Detected by Bone Scanning—Gary F. Gates MD, Long Beach. Premature closure of cranial sutures in children (craniosynostosis) may lead to grotesque skull deformities, mental retardation and blindness. Early detection and treatment are imperative if permanent brai damage is to be prevented. As clinical and radiographi examinations may fail to detect early closure, skull imagin with radiofluorine (^{18}F) or ^{99m}Tc Polyphosphate was performed in a group of children to demonstrate cranial sutur growth abnormalities.

This exhibit shows the results of this study. Normal an abnormal skulls are readily differentiated and in som instances the cranial scan yielded information that was no obtainable by either radiographic or clinical examinatio

pidemiology of Lead Poisoning—Colin T. Greenlaw, MD, Sacramento. Various exhibit specimens illustrating sources of lead and ways it can be inadvertently introduced into the human body. Included will be a container of simulated gasoline, ceramic ware, paint, etc., along with appropriate posters. There will be posters and photographs describing possible methods of transmission of elemental lead to the human body, and instruments which demonstrate actual on-site measuring of lead content in blood and in household and industrial materials.

valuation of Cromolyn Sodium in Pollen-Induced Asthma—Daniel H. Goodman, MD, Portland, Oregon. This exhibit illustrates and explains the presumed method of action of cromolyn sodium in animals. Also described are double-blind trials of cromolyn sodium in pollen-sensitive asthmatic children and adults.

ncomplete Pulmonary Infarction: A Diagnostic Challenge—Oscar J. Balchum, MD, Los Angeles. Characteristic symptom complex, depicting diagnostic procedure, clinicopathology, possible sequelae and patient management will be presented.

ndications for Surgery in Rheumatoid Arthritis—Roger Levy, MD, New York City. This exhibit is sponsored by the Committee on Arthritis of the American Academy of Orthopaedic Surgery. Posters and illustrations will present indications for surgical treatment of rheumatoid patients.

edical Imaging Using Acoustical Holography—A. F. Metherell, PhD, Irvine. A medical imaging system has been developed which uses sound waves to acoustically illuminate the soft tissues and organs in the human abdomen. The sound waves are recorded on film, not as a conventional image, but as a hologram which is capable of reconstructing a three-dimensional image of the entire acoustically illuminated body. This enables any image plane to be focused upon and visualized as a two-dimensional picture. This exhibit will describe the system and show clinical results obtained at University of California, Irvine, California College of Medicine.

inimal Brain Dysfunction: Stability Through Medication—Leon Oettinger, Jr., MD, San Marino. This exhibit draws upon the author's 25 years' experience in diagnosing and treating children with minimal brain dysfunction. Diagnosis, treatment, and effects of treatment are discussed.

ew Clinical Studies on the Treatment of the Allergic Response—Cathryn D. Evans, Palo Alto.

Orthotic Management in Myelodysplasia—John V. Banta, MD, San Diego. Review of orthotic principles, beginning with birth assessment by application of Lorbers Sheffield criteria. Management principles outline pre-walker and fully ambulatory bracing patterns correlated to the level of neurological deficit.

Psoriasis Day Care Center—David L. Cram, MD, San Francisco. On February 5, 1973, the Dermatology Department of the University of California Hospitals and Clinics, San Francisco, opened a Psoriasis Day Care Center, the first such treatment facility in the United States. The center is a hospital where patients with severe psoriasis are treated intensively during the day and allowed to return home at night. The concept, which originated with Professor Grupper of the Rothschild Foundation, Paris, has distinct advantages over conventional hospital care.

Self-Instructional Materials for Ophthalmology—Gary M. Arsham, MD, San Francisco. This exhibit shows a unique series of mannequins designed for realistic simulation of ophthalmoscopy. Practitioners will be able to test their own proficiency at handling the ophthalmoscope and at recognizing and describing fundus details. They will also be able to follow short interactive tape-slide demonstrations on normal and abnormal fundus aspects. Another simulation device allows the practitioner to test his skill in performing and interpreting the cover test for the detection of strabismus. Tape-slide presentations will provide background information on strabismus, glaucoma, tonometry, ocular emergencies and neuro-ophthalmology.

Sleep Disorders: Evaluation and Treatment—Anthony Kales, MD, Hershey, Pennsylvania. Findings from sleep research which are of direct and practical value in the evaluation and treatment of patients with sleep disorders.

Subcutaneous Mastectomy for Chronic Cystic Disease of the Breast—Vincent R. Pennisi, MD, San Francisco. This exhibit describes a treatment by subcutaneous mastectomy for moderate to severe chronic cystic disease of the breasts. Concrete evidence of the association of certain forms of fibrocystic disease and carcinoma will be presented. Included also will be the indications for subcutaneous mastectomy and several pictures describing the procedure and its complications.

Trigeminal Neuralgia (Tic Douloureux)—Mechanisms and Treatment—Donald J. Dalessio, MD, La Jolla. This exhibit describes the physiologic mechanisms of trigeminal neuralgia and speculates on possible causes. The connection between facial trigger zones, activities which may precipitate an attack, and neural pathways are illustrated and discussed. Characteristics of typically affected patients and the results of treatment with carbamazepine are described.

Visual Screening in Pre-School and School-Aged Children—Byron H. Demorest, MD, Sacramento. This exhibit will consist of recommendations by the California Association of Ophthalmology and the Northern California Society for the Prevention of Blindness for pre-school and school vision screening. Demonstration materials will be available in addition to a narrative picture presentation of the indications, methods and findings of visual screening in young children.

Visit the Technical Exhibits

Imperial Ballroom
and
Franciscan Room

MARCH 2-5, 1974
9:00 a.m. to 5:00 p.m.

Preregistration Forms

Non-CMA members please note: There is a $10 registration fee for the Annual Session. This fee is for admittance to the assembly and does not cover any of the following special meetings. (CMA members need not pay this $10 general admittance fee.)

Allergy Section

Luncheon and Business Meeting with the California Society of Allergy and Clinical Immunology

SUNDAY, MARCH 3, 12:00 noon

$10

Please reserve ________ tickets for:

Name ____________________

Address ____________________

City ____________________ Zip ________

Please make check payable to: CMA Section on Allergy

Return this application with total remittance to:

JULIAN L. HARWELL, MD
960 East Green Street, Suite L-5
Pasadena, CA 91106

Joint Meeting: Sections on Anesthesiology and Chest Diseases

Luncheon Speaker: EDWARD A. GAENSLER, MD
Professor of Surgery, Harvard University School of Medicine

SUNDAY, MARCH 3, 12:30 pm

$10

Please reserve ________ tickets for:

Name ____________________

Address ____________________

City ____________________ Zip ________

Please make check payable to: CMA Sections on Anesthesiology and Chest Diseases

Return this application with total remittance to:

WILBUR Y. HALLETT, MD
2701 West Alameda Avenue
Burbank, CA 91505

General Surgery Section

Joint luncheon meeting with American College of Surgeons
Luncheon Speaker: RUPERT B. TURNBULL, Jr., MD, Cleveland

MONDAY, MARCH 4, 12:00 noon

$10

Please reserve ________ tickets for:

Name ____________________

Address ____________________

City ____________________ Zip ________

Please make check payable to: CMA Section on General Surgery

Return this application with total remittance to:

EARL F. WOLFMAN, JR., MD
Dept. of Surgery, TB-154
UC-Davis School of Medicine
Davis, CA 95616

Obstetrics and Gynecology Section

Luncheon reservation

MONDAY, MARCH 4, 12:15 pm

$10

Please reserve ________ tickets for:

Name ____________________

Address ____________________

City ____________________ Zip ________

Please make check payable to: CMA Section on Obstetric and Gynecology

Return this application with total remittance to:

CHARLES WEBER, MD
7300 Girard Avenue, Suite 203
La Jolla, CA 92037

Plastic Surgery Section

Special Conference Reservation (Laboratory)
(Enrollment limited to 40 physicians)

MONDAY, MARCH 4, 10:00 am

$25

Please enroll ________ in the Special Conference on Plasti Surgery

Name ____________________

Address ____________________

City ____________________ Zip ________

Please make check payable to: CMA Section on Plasti Surgery

Return this application with total remittance to:

ROGER FRIEDENTHAL, MD
2211 Post Street
San Francisco, CA 94115

Ophthalmology Section

Special Conference and Luncheon Reservation

SATURDAY, MARCH 2, 10:00 am and
SUNDAY, MARCH 3, 9:00 am
$10 for each session

Please reserve ________ tickets for Saturday, March 2 and ________ tickets for Sunday, March 3 for:

Name ____

Address ____

City ______________________________ Zip __________

Please make check payable to: CMA Section on Ophthalmology

Please register by February 15, 1974. No refunds will be made after this date.

Return this application with total remittance to:

BRUCE SPIVEY, MD
Department of Ophthalmology
Pacific Medical Center
P.O. Box 7999
San Francisco, CA 94122

Human Sexuality and Other Medical Complications

Special Conference and Luncheon Reservation

SATURDAY, MARCH 2
$25

Please reserve ________ tickets for:

Name ____

Address ____

City ______________________________ Zip __________

Please make check payable to: CMA Venereal Disease Task Force

Return this application with total remittance to:

GWENN BURNHAM
California Medical Association
731 Market Street
San Francisco, CA 94103

Alcoholism and Drug Dependence

Special Conference and Luncheon Reservation

SUNDAY, MARCH 3
$15

Please reserve ________ tickets for:

Name ____

Address ____

City ______________________________ Zip __________

Please make check payable to: CMA Committee on Alcoholism and Other Drug Dependence

Return this application with total remittance to:

GAIL JARA
California Medical Association
731 Market Street
San Francisco, CA 94103

Federated Meeting:

American College of Physicians (Northern California and Nevada) and Internal Medicine Section

Special Conference and Luncheon Reservation

FRIDAY, MARCH 1 (afternoon session)
SATURDAY, MARCH 2 (all day, includes luncheon)
$20

Please reserve ________ tickets for:

Name ____

Address ____

City ______________________________ Zip __________

Please make check payable to: American College of Physicians

Return this application with total remittance to:

MAURICE FOX, MD
300 Homer Avenue
Palo Alto, CA 94301

Visit the
Scientific and Organizational Exhibits

Garden Lane, California Room
and
North Lounge

MARCH 2-5, 1974
9:00 a.m. to 5:00 p.m.

THOMAS ELMENDORF, MD
President

STANLEY A. MOORE, MD
President-Elect

Officers and Delegates

GENERAL OFFICERS

Thomas Elmendorf, Willows	*President*
Stanley A. Moore, San Diego	*President-Elect*
Joseph F. Boyle, Los Angeles	*Speaker, House of Delegates*
Henry V. Eastman, Tustin	*Vice-Speaker, House of Delegates*
E. Kash Rose, Napa	*Chairman of the Council*
Frederick W. Ackerman Pleasant Hill	*Vice-Chairman of the Council*
Jean F. Crum, Downey	*Immediate Past President*
Helen B. Weyrauch, San Francisco	*Secretary*
Malcolm S. M. Watts, San Francisco	*Editor*
Robert L. Thomas	*Executive Director*
Hassard, Bonnington, Rogers & Huber	*Legal Counsel*

House of Delegates

TOTAL VOTING MEMBERS (323*)

OFFICERS
Non-Voting (9)

Thomas Elmendorf, Willows	President
Stanley A. Moore, San Diego	President-Elect
Joseph F. Boyle, Los Angeles	Speaker, House of Delegates
Henry V. Eastman, Tustin	Vice-Speaker, House of Delegates
E. Kash Rose, Napa	Chairman of the Council
Frederick W. Ackerman, Pleasant Hill	Vice-Chairman of the Council
Jean F. Crum, Downey	Immediate Past President
Helen B. Weyrauch, San Francisco	Secretary
Malcolm S. M. Watts, San Francisco	Editor

COUNCILORS
Voting (27)

FIRST DISTRICT—	
Office No. 1, Gladden V. Elliott	(1976)
Office No. 2, Simon C. Brumbaugh, Jr.	(1974)
SECOND DISTRICT—Nicholas P. Krikes	(1974)
THIRD DISTRICT—	
Office No. 1, Fred M. Kay	(1975)
Office No. 2, New position to be filled at 1974 Annual Session	
FOURTH DISTRICT—	
Office No. 1, Philip F. Voigt	(1974)
Office No. 2, Jokichi Takamine	(1974)
Office No. 3, Ralph M. Milliken	(1976)
Office No. 4, Samuel Horowitz	(1974)
Office No. 5, William P. Frank	(1975)
Office No. 6, Jack E. McCleary	(1976)
Office No. 7, George C. Andersen	(1974)
Office No. 8, Harold E. Wilkins	(1975)
Office No. 9, Frank A. Rogers	(1976)
FIFTH DISTRICT—Charles M. Hair	(1976)
SIXTH DISTRICT—	
Office No. 1, Arthur F. Howard	(1975)
Office No. 2, Robert K. Salter	(1974)
SEVENTH DISTRICT—	
Office No. 1, Dan W. Clark	(1976)
Office No. 2, John T. Saidy	(1974)
EIGHTH DISTRICT—	
Office No. 1, Albert G. Clark	(1975)
Office No. 2, Sanford E. Feldman	(1976)
NINTH DISTRICT—	
Office No. 1, Carl Goetsch	(1975)
Office No. 2, Frederick W. Ackerman	(1976)
TENTH DISTRICT—E. Kash Rose	(1976)
ELEVENTH DISTRICT—Orrin S. Cook	(1975)
TWELFTH DISTRICT—Forrest J. Grunigen	(1975)
SCIENTIFIC BOARD REPRESENTATIVE—C. John Tupper	(1976)

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*Total to be increased with addition of House Staff Delegates

SCIENTIFIC BOARD
Ex officio, Non-voting (21)

Delegates	Alternates
Tupper, C. John, Chairman	Bittner, Donald L.
Ashley, Franklin L.	Brumbaugh, Simon C., Jr.
Banta, John V.	Gamble, John
Brockman, Seymour J.	Gonda, Thomas A.
Cailliet, Rene	Gross, George A.
Connolly, John E.	Hall, Albert D.
Dutra, Frank R.	Halter, Bert L.
Einstein, Hans E.	Hatoff, Alexander
Gee, Vernon R.	Hibbard, Lester T.
Gillogley, Walter J.	Kaye, Ronald L.
Graham, James H.	Manning, Phil R.
Harris, Robert M.	Martin, James W.
Hodges, Frederick B.	McGann, Benson
Holden, Herbert A.	Ottenheimer, Edward J.
Leonards, Richard	Pace, J. Blair
Meleyco, Leo N.	Robinson, Saul J.
Opfell, Richard W.	Selzer, Arthur
Palmer, John M.	Vandervoort, Herbert E.
Podosin, Robert L.	Vacancy
Rolf, Bruce B.	Vacancy
Straatsma, Bradley R.	Vacancy

PAST PRESIDENTS
Ex officio, Non-voting (23)

Molony, William R., Sr.	1942
Schaupp, Karl L., Sr.	1943
Cline, John W.	1947
Askey, E. Vincent	1948
Cass, Donald	1950
Green, John W.	1953
Morrison, Arlo A.	1954
Shipman, Sidney J.	1955
MacDonald, Frank A.	1957
West, Francis E.	1958
Reynolds, T. Eric	1959
Foster, Paul D.	1960
Bostick, Warren L.	1961
Sherman, Samuel R.	1963
Doyle, James C.	1964
Teall, Ralph C.	1965
MacLaggan, James C.	1966
Morrison, John G.	1967
Todd, Malcolm C.	1968
Miller, Albert G.	1969
Burnett, Ralph W.	1970
Fenlon, Roberta F.	1971
Crum, Jean F.	1972

HONORARY PAST PRESIDENTS
Ex officio, Non-voting (2)

Murray, Dwight H., Sr.

Wilbur, Dwight L.

CMA DELEGATION TO THE AMA
Ex officio Non-voting (25)

Delegation Office Number	Delegate	Alternate
	FIRST DISTRICT	
1	**James C. McLaggan** San Diego 1-1-74 to 12-31-75	**Stewart Dadmun** San Diego 1-1-73 to 12-31-74
2	**Elmer C. Werner** El Centro 1-1-74 to 12-31-75	*Office will be 1-1-74 to 12-31-75
	SECOND DISTRICT	
3	**Herman H. Stone** Riverside 1-1-73 to 12-31-74	**Nicholas P. Krikes** San Bernardino 1-1-74 to 12-31-75
	THIRD DISTRICT	
4	Election results not available at press time (Offices will be 1-1-74 to 12-31-75)	
	FOURTH DISTRICT	
5	**Jean F. Crum** Downey 1-1-73 to 12-31-74	**David B. Horner** Inglewood 1-1-74 to 12-31-75
6	**Frank A. Rogers** Whittier 1-1-74 to 12-31-75	**Walter Buerger** Covina 1-1-73 to 12-31-74
7	**William F. Quinn** Los Angeles 1-1-73 to 12-31-74	**Jokichi Takamine** Los Angeles 1-1-73 to 12-31-74
8	**Joseph P. O'Connor** Pasadena 1-1-74 to 12-31-75	**H. Russell Fisher** Glendale 1-1-73 to 12-31-74
9	**Homer Pheasant** Los Angeles 1-1-73 to 12-31-74	**Ralph M. Milliken** Los Angeles 1-1-74 to 12-31-75
10	**Marvin J. Shapiro** Encino 1-1-74 to 12-31-75	**Jack E. McCleary** Sherman Oaks 1-1-73 to 12-31-74
11	**Edward J. Wiater†** Long Beach Fall-73 to 12-31-74	**Donald R. Fitch** Los Angeles 1-1-73 to 12-31-74
12	**Joseph F. Boyle** Los Angeles 1-1-73 to 12-31-74	**Raymond N. F. Killeen** Los Angeles 1-1-74 to 12-31-75
13	**A. J. Murrieta, Jr.** Los Angeles 1-1-73 to 12-31-74	**David I. Olch** Los Angeles 1-1-74 to 12-31-75
	FIFTH DISTRICT	
14	**Harry J. Fryer** San Luis Obispo 1-1-74 to 12-31-75	**R. John Rutten** Santa Barbara 1-1-73 to 12-31-74
	SIXTH DISTRICT	
15	**Robb Smith** Orange Cove 1-1-73 to 12-31-74	**Arthur F. Howard** Fresno 1-1-74 to 12-31-75
16	**Ralph W. Burnett** Bakersfield 1-1-73 to 12-31-74	**David S. Ardell** Bakersfield 1-1-73 to 12-31-74
	SEVENTH DISTRICT	
17	**Leon P. Fox** San Jose 1-1-73 to 12-31-74	**R. Hewlett Lee** Palo Alto 1-1-73 to 12-31-74
18	**John T. Saidy** San Mateo 1-1-74 to 12-31-75	**Howard W. Lindsey** San Mateo 1-1-74 to 12-31-74
	EIGHTH DISTRICT	
19	**George K. Herzog, Jr.** San Francisco 1-1-74 to 12-31-75	**Xavier O. Barrios** San Francisco 1-1-74 to 12-31-75
20	**Edward T. Kelley** San Francisco 1-1-74 to 12-31-75	**Brad Cohn** San Francisco 1-1-74 to 12-31-75
	NINTH DISTRICT	
21	Election results not available at press time (Offices will be 1-1-74 to 12-31-75)	
22	**John G. Morrison** San Leandro 1-1-73 to 12-31-74	**Frederick Ackerman** Pleasant Hill 1-1-73 to 12-31-74
	TENTH DISTRICT	
23	**Walter H. Brignoli** St. Helena 1-1-73 to 12-31-74	**Raymond C. Anderson** Santa Rosa 1-1-74 to 12-31-75
	ELEVENTH DISTRICT	
24	**Ralph C. Teall** Sacramento 1-1-74 to 12-31-75	**James H. Yant** Sacramento 1-1-73 to 12-31-74
	AT-LARGE‡	
25	**Robert C. Combs** Irvine 1-1-73 to 12-31-74	**Thomas Elmendorf** Willows 1-1-74 to 12-31-75

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*Election result not available at press time

†Filling unexpired term of Malcolm C. Todd

‡At the expiration of "At-large" terms, the offices revert to District 3, i.e., Delegate to District 3 as of 1-1-75, Alternate to District 3 as of 1-1-76.

First District
Imperial and San Diego Counties

Second District
Inyo, Mono, Riverside and San Bernardino Counties

Third District
Orange County

Fourth District
Los Angeles County

Fifth District
San Luis Obispo, Santa Barbara and Ventura Counties

Sixth District
Amador, Calaveras, Fresno, Kern, Kings, Madera, Mariposa, Merced, San Joaquin, Stanislaus, Tulare, and Tuolumne Counties

Seventh District
Monterey, San Benito, San Mateo, Santa Clara and Santa Cruz Counties

Eighth District
San Francisco County

Ninth District
Alameda and Contra Costa Counties

Tenth District
Del Norte, Humboldt, Lake, Marin, Mendocino, Napa, Solano and Sonoma Counties

Eleventh District
Alpine, Butte, Colusa, El Dorado, Glenn, Lassen, Modoc, Nevada, Placer, Plumas, Sacramento, Shasta, Sierra, Siskiyou, Sutter, Tehama, Trinity, Yolo and Yuba Counties

Twelfth District
Forty First Medical Society

ELECTED DELEGATES (288)

ALAMEDA-CONTRA COSTA (22)

(Not available at press time)

BUTTE-GLENN (2)

(Not available at press time)

FORTY FIRST (2)

(Not available at press time)

FRESNO (6)

(Not available at press time)

HUMBOLDT-DEL NORTE (2)

Delegates	Alternates
Braafladt, Halvor J.	Grigorieff, Paul
Loring, Theodore W.	Raila, Frank

IMPERIAL (2)

Delegates	Alternates
Jaquith, George	Fosgate, O. E.
Schoensee, Burke	Werner, Elmer C.

INYO-MONO (2)

Delegates	Alternates
Hough, Victor	Ungersma, John A.
Vacancy	Vacancy

KERN (4)

(Not available at press time)

KINGS (2)

(Not available at press time)

LASSEN-PLUMAS-MODOC-SIERRA (2)

(Not available at press time)

LOS ANGELES (89)

Delegates	Alternates
Adams, Donald A.	Alban, Seymour L.
Affley, Harry J.	Alexakis, Peter G.
Alter, Marvin S.	Baker, Francis J.
Amerongen, Frederick K.	Belt, Robert L.
Aquila, S. J.	Bertolino, James
Asher, Leonard M.	Birnberg, Victor
Axelrod, Bernard	Blackman, Burton T.
Baker, Jack W.	Bland, Stephen L.
Basque, William D.	Bradley, Gerald H.
Bergreen, Stanley W.	Bruckner, Sherman H.
Blood, William B.	Butler, Edwin
Bowen, Gordon T.	Carney, Padraig
Brennan, James E.	Chusid, Lawrence A.
Buehler, George S.	Cooperman, Howard
Buerger, Walter R.	Creary, Ludlow B.
Butler, R. Melvin	Critchlow, Francis B.
Carroll, Robert L.	Dahl, David J.
Chasan, Fred	Dashe, Alfred M.
Chiang, Ching H.	Dickes, Richard E.
Cope, Jerome A.	Diehl, John W.
Crumrine, Martin H.	Diess, Neil E.
del Junco, Tirso	Edwards, John W.
DeMangus, Robert X.	Elconin, Kenneth B.
Donoghue, Charles K.	Farfel, A. Beryl
D'Orazio, Edward	Fortier, John J.
Dorn, Robert M.	Furman, Morris J.
Ellerbeck, Walter P.	Greenberg, Paul M.
Evashwick, George	Gualtieri, Vincent
Feinberg, Munish	Guiss, Lewis W.
Fields, Albert	Hart, Rinard Z.
Ford, James H.	Hartleip, Duane L.
Frank, William P.	Heiser, Saul
Fritz, Samuel H.	Hoffman, Warren F.
Gordon, Irving J.	Holtz, Marvin J.
Greco, Donald J.	Hoyos, Jorge
Harter, Melvin M.	Hyman, William
Haskell, M. M.	Japenga, Jack W.
Hassen, Mitchell	Jenkins, Charles E.
Hemsley, Hubert L.	Jones, Henry A.
Hill, Harry E.	Karlan, Mitchell S.
Hoffmann, Peter L.	Karns, Robert M.
Horner, David B.	Kaspar, Friedrich H.
Johnson, Robert M.	Katz, Edward E.
Kaminski, Kenneth L.	Keenan, Charles E., Jr.
Kaufman, Gene B.	Kolpack, Marvin W.
Kaufmann, Bertram J., Jr.	Krause, Melvyn H.
Ketcham, Burton E., Jr.	Kuhn, Robert
Killeen, Raymond N. F.	Landon, Charles W.
Klein, E. Philip	Llanos, Miguel A.
Kremen, Samuel	Marr, James C., Jr.
Kugel, Arthur I.	Mazurek, Richard J.
Lau, Michael W.	McElwee, Charles B.
Lopez, Charles J.	McRae, John A.
McCaffery, James M.	Menze, Jackson S.
Mailman, Richard H.	Michels, Arthur G.
Martini, M. Michael	Mizener, Wilson
May, Lewis H. V.	Moore, Rolet A.
Meine, Emile L., Jr.	Morgan, Henry G.
Miller, Richard D.	Murphy, Terrence J.
Milliken, Ralph M.	Nehorayan, S. Saul
Murrieta, A. J., Jr.	Nishizawa, Akira
Neuenschwander,	Noguchi, Thomas T.
Robert S.	Okie, Theodore B.
Newhouse, Robert M.	Pallette, Edward M.
Odou, Eugene R.	Reager, Lauren L.
Olch, David I.	Redewill, Francis H., Jr.
Palmer, Jay J.	Sanchez, Alphonso R.
Penka, Ernest J.	Schmit, Robert A.
Penn, Sidney W.	Seidman, Donald R.
Pettit, Richard D.	Sewak, John H.
Pollack, John V.	Sibley, Willie F.
Richards, Melvin R.	Siegel, Joseph A.
Rothenberg, Sanford F.	Slater, Roger A.
Rockney, Robert E.	Spierer, Eugene
Rubell, Earl B.	Stanton, Ernest M.
Rudy, Norman E.	Stauffer, Floyd R.
Smith, Thayer A.	Steen, Alan M.
Todt, Jack C.	Tashma, Albert
Trumbull, William E.	Todd, William H.
van Adelsberg, Stephan B.	Trafas, Peter C.
Wandling, Harold S.	Tudbury, Patricia B.
Weil, William S.	Valvo, Carlton F.
Weiss, Benjamin J.	Watson, Robert L., Jr.
Wiater, Edward J.	Westerbeck, Charles W.
Wigton, John R.	White, John R.
Williams, Henry S.	Wong, Alton S. K.
Wong, Thomas A.	Yamaguchi, Donald M.
Wright, Carter R., Jr.	Zinn, Willard J.
Wunderlich, Edwin E.	Zwemer, Theodore W.
Zinn, Alexander N.	

MARIN (4)

Delegates	Alternates
Costanza, David	Belknap, Marjorie
Lee, John R.	Franzblau, Michael
Tavel, Frank	Lesco, Clarence
White, A. Halnan	Weden, Elmer, Jr.

MENDOCINO-LAKE (2)

Delegates	Alternates
Hamlin, Mervyn	Cook, Robert A.
Waring, William W.	Nicholson, Thomas

MERCED-MARIPOSA (2)

Delegates	Alternates
Anglin, John V.	Patterson, Kalfus W.
Faber, Dorian R.	Rugani, Peter R.

MONTEREY (4)

(Not available at press time)

NAPA (2)

Delegates	Alternates
Hemphill, Arthur C.	Ehrlich, Harry
Queary, Charles H.	Waechtler, Herbert W.

ORANGE (16)

(Not available at press time)

PLACER-NEVADA (2)

(Not available at press time)

RIVERSIDE (5)

(Not available at press time)

SACRAMENTO (9)

(Not available at press time)

SAN BENITO (2)

Delegates	Alternates
Badke, Robert T.	Vacancy
Kirch, Joseph	Vacancy

SAN BERNARDINO (7)

Delegates	Alternates
Harer, W. Benson, Jr.	Allen, Byron
Hendrickson, Merlin A.	Ballard, Ross L.
Miano, Ben D. A.	Carmack, Charles
Mortensen, John	Gillespie, James
Moseley, Wendell	Kirshbaum, Robert
Sterling, Allen	McAllister, John
Wake, Donald	Taurek, Jerome

SAN DIEGO (17)

(Not available at press time)

SAN FRANCISCO (19)

Delegates	Alternates
Barrios, Xavier O.	Allen, David W.
Bender, William T.	Biskind, Gerson R.
Cohn, Brad	Davis, Harold
Cook, Robert E.	Dulay, Fernando V.
Driscoll, John A.	Foster, Sidney E.
Lee, Jane F.	Frenkenberg, Andre M. M.
Levin, Sheldon M.	Franzi, Antonio J.
Kelley, Edward T.	King, Charles
Lindner, Harold H.	McFadden, Samuel D.
Palmer, Richard J.	Molyneaux, Glenn
Phipps, James W.	Noltimier, Louis A.
Pillsbury, Philip L.	Oscherwitz, Mark
Rixford, Emmet L.	Paver, Robert
Robinson, Saul J.	Pevehouse, Byron C.
Schaffarzick, Ralph W.	Salomon, Maurice S.
Solari, Rafael A.	Saunders, John B. deC. M.
Wayburn, Edgar	Scholten, Paul
Weinreb, Irwin	Sherman, Robert S., Jr.
Wray, H. Wesley	White, Laurens P.

SAN JOAQUIN (4)

Delegates	Alternates
Clark, Stanley A., Jr.	Browne, Robert T.
McNally, John T.	Hoff, Helmuth
Wass, Warren	Kimball, John
Williams, George	Shinn, William

SAN LUIS OBISPO (2)

Delegates	Alternates
Cletsoway, Richard W.	Jorgensen, Jerren
Osibin, Willard S.	McAdams, Brendan V.

SAN MATEO (8)

Delegates	Alternates
Bell, Leo S.	Beames, Ranulf P.
Geraci, Charles L.	Chamberlain, Alfred D.
Hart, Ward L.	Feinstein, Myron S.
Healy, Francis A.	Hansen, James R.
Hills, Oscar	Johnson, Harold P., Jr.
Kohn, Martin M.	Marquette, Richard H.
Lindsey, Howard W.	Nagumo, Saburo
Richanbach, Henry S.	Richards, Marvin D.

SANTA BARBARA (5)

(Not available at press time)

SANTA CLARA (15)

Delegates	Alternates
Armstrong, Frederick S.	Austin, Glenn
Boice, Clyde L.	Bright, Ross D.
Burnett, Robert D.	Dolan, Michael P.
Drinker, Henry R., Jr.	Elliott, Hugh W.
Fox, Leon P.	Gherini, Allan J.
Giansiracusa, Frank	Kornfield, Harrison J.
Grossman, Maurice	Lippe, Philipp M.
Kaufman, S. Fred	Rappaport, Maurice
Lee, R. Hewlett	Reeves, William
Liston, Edward	Rodenbaugh, F. Hase
McCort, James J.	Truitt, Robert B.
Neubauer, Ivan	Upton, Hubert M.
O'Neill, Robert J.	Whelan, Harry G.
Rowles, Donald	Williams, J. Hicks
Scarborough, C. Gerald	Zlotnick, David

SANTA CRUZ (3)

Delegates	Alternates
Jones, Robert C.	Dunn, Bruce L.
King, John W.	Field, John A.
Nelson, Carl	Liddicoat, Douglas

SHASTA-TRINITY (2)

(Not available at press time)

SISKIYOU (2)

Delegates	Alternates
Christy, John R.	Klatt, Lloyd I.
Knudson, Stephen	Lund, Johanna E.

SOLANO (2)

Delegates	Alternates
Gullock, Alvin H.	Miller, John C.
Lonsdale, Howard C.	Vincent, Keith E.

SONOMA (3)

Delegates	Alternates
Anderson, Raymond C.	Archambeau, Paul L.
Lones, Frank E.	Cary, Stephen C.
Olney, John M.	Swensen, Alan D.

STANISLAUS (3)

Delegates	Alternates
Bigelow, Wayne B.	Baker, Perren
Pote, William	McKibben, J. Warren
Purvis, Robert W.	Nyegaard, Roland C.

TEHAMA (2)

Delegates	Alternates
Gumm, Melvin	Greene, Frank P.
Jourdan, H. W.	Wolfe, L. E.

TULARE (3)

(Not available at press time)

VENTURA (4)

Delegates	Alternates
Gstettenbauer, Joseph F.	Fingerle, Arthur C.
Huff, W. Cloyce	Huckins, A. Ray
Spoto, Russell C.	Loft, Richard S.
Stoutz, Henry L.	Reach, Charles

YOLO (2)

(Not available at press time)

YUBA-SUTTER-COLUSA (2)

(Not available at press time)

Visit the Technical Exhibits

Imperial Ballroom

and

Franciscan Room

MARCH 2-5, 1974

9:00 a.m. to 5:00 p.m.

1974 Annual Session

House of Delegates

AGENDA

Hilton Plaza, San Francisco Hilton Hotel

Joseph F. Boyle, Los Angeles	*Speaker*
Henry V. Eastman, Tustin	*Vice-Speaker*
Helen B. Weyrauch, San Francisco	*Secretary*

SATURDAY, MARCH 2, First Meeting

REGISTRATION—12:00 noon
MEETING STARTS—1:00 p.m. Sharp

1. Call to order (Invocation and Pledge of Allegiance)
2. Announcement of Reference Committees*
    - Committee on Credentials
    - Reference Committee A—Community and Environmental Health
    - Reference Committee B-1—Government Medical Programs
    - Reference Committee B-2—Government Medical Programs
    - Reference Committee C-1—Medical Economics, Insurance and Prepayment
    - Reference Committee C-2—Medical Economics, Insurance and Prepayment
    - Reference Committee D-1—Scientific and Educational Activities
    - Reference Committee D-2—Scientific and Educational Activities
    - Reference Committee E-1—Professional and Public Relations
    - Reference Committee E-2—Professional and Public Relations
    - Reference Committee F—Finance
    - Reference Committee G—Constitution and Bylaws
    - Reference Committee H—Blue Shield of California
3. Miscellaneous Announcements
4. Honored Guests
5. Report of the Committee on Credentials, and Organization of the House of Delegates—Roll Call
6. Recognition of President of Woman's Auxiliary to the CMA—Mrs. Thomas A. Gibson
7. Address by President—Thomas Elmendorf
8. Report of the President—Thomas Elmendorf
9. Report of the President-Elect—Stanley A. Moore
10. Report of the Speaker and Vice-Speaker of the House of Delegates—Joseph F. Boyle and Henry V. Eastman
11. Report of the Trustees of the California Medical Association—Thomas Elmendorf
12. Report of the Physicians' Benevolence Fund, Inc.—Thomas Elmendorf
13. Report of the Secretary—Helen B. Weyrauch
14. Report of the Editor—Malcolm S. M. Watts
15. Report of the Executive Director—Robert L. Thomas
16. Report of Legal Counsel—Hassard, Bonnington, Rogers & Huber
17. Report of the Executive Committee—Thomas Elmendorf
18. Report of the Council—E. Kash Rose, Chairman
19. Report of Blue Shield of California Trustees—Marvin J. Shapiro, Chairman
20. Reports of Commissions
21. Reports of other Committees
22. Old and unfinished business
23. New business
24. Adjournment

TUESDAY, MARCH 5, Second Meeting

REGISTRATION—12:00 noon
MEETING STARTS—1:30 p.m.
(To be recessed and reconvened at 9:00 a.m., Wednesday, March 6)

1. Call to order
2. Supplemental Report of Credentials Committee—Roll Call
3. Address by President-Elect—Stanley A. Moore
4. Introduction of President-Elect of Woman's Auxiliary to the CMA—Mrs. Harry S. Dvorsky
5. Secretary's announcement of Council's selection of time and place for the 1975 Annual Session
6. Election of Officers
7. Report of Reference Committee G (Constitution and Bylaws)
8. Announcement of nominations of Delegates and Alternates to the American Medical Association
9. Election of Blue Shield of California Trustees
10. Reports of Reference Committees
11. Unfinished business
12. New business
13. Presentation of Officers
14. Adjournment

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*Subject to revision

Proposed CMA Constitutional Amendments

FOR ACTION IN 1974

Four Constitutional amendments were introduced in the 1973 House of Delegates. Under the terms of the Constitution, these amendments must lie on the table until the next regular meeting of the House of Delegates.

These proposed amendments are shown here for the information of the membership. In addition, the proposed Constitutional amendments are required to be printed in two issues of California Medicine before they come before the House of Delegates for action.

* * *

ARTICLE IV, SECTION 6—BENEVOLENCE FUND

Introduced by: Council
Representing: Council
Author: John T. Saidy, MD

Constitutional Amendment 1-73
Committee G

Resolved: That Article IV, Section 6.—Benevolence Fund, be amended by deleting the words in brackets, and adding the words in italics, so that the section shall now read:

"At least [$1.00] *$0.50* out of the annual dues paid by each active member of the Association shall be allocated to the Physicians' Benevolence Fund, Inc., a Corporation, and shall be used for the purposes as set forth in that Corporation's Articles and Bylaws."

ACTION: Tabled for one year; to be acted upon at the 1974 meeting of the House of Delegates.

* * *

FORMATION OF NEW COUNCILOR DISTRICT

Introduced by: 11th District Delegation
Author: John R. Heckman, MD

Constitutional Amendment 2-73
Committee G

Resolved: That Article III, Part B, Section 10 of the CMA Constitution be amended as follows: (deletions in brackets, additions in italics)

Section 10.—Councilor Districts

There are [12] *13* Districts as follows:

District Number One, comprising San Diego and Imperial Counties.

District Number Two, comprising Riverside, San Bernardino, Mono and Inyo Counties.

District Number Three, comprising Orange County.

District Number Four, comprising the County of Los Angeles.

District Number Five, comprising Ventura, Santa Barbara and San Luis Obispo Counties.

District Number Six, comprising Alpine, Amador, Kern, Kings, Tulare, Fresno, Madera, Mariposa, Merced, Stanislaus, San Joaquin, Calaveras and Tuolumne Counties.

District Number Seven, comprising Monterey, San Benito, Santa Cruz, Santa Clara and San Mateo Counties.

District Number Eight, comprising San Francisco County.

District Number Nine, comprising Alameda County and Contra Costa County.

District Number Ten, comprising Marin, Solano, Napa, Sonoma, Lake, Mendocino, Humboldt and Del Norte Counties.

District Number Eleven, comprising Sacramento *and* El Dorado, [Placer, Nevada, Sierra, Yuba, Sutter, Yolo, Colusa, Glenn, Butte, Plumas, Tehama, Trinity, Shasta, Lassen, Modoc and Siskiyou] Counties.

District Number Twelve, *comprising Placer, Nevada, Sierra, Yuba, Sutter, Yolo, Colusa, Glenn, Butte, Plumas, Tehama, Trinity, Shasta, Lassen, Modoc and Siskiyou Counties.*

District Number Thirteen, consisting of any society which is not limited as to geographical area, or the area of which overlaps the area covered by one or more existing component societies;

such society and its members shall not be considered to be members of any other councilor district.

ACTION: Tabled for one year; to be acted upon at the 1974 meeting of the House of Delegates.

* * *

ARTICLE IV, SECTION 6—"BENEVOLENCE FUND"

Introduced by: Reference Committee "G"

Constitutional Amendment 3-73
Committee G

Whereas, the Benevolence Fund is now at sufficient size that it is self-supporting; and

Whereas, the addition of new monies to the Benevolence Fund is more properly placed in the immediate control of the House of Delegates as in the matter of dues; now, therefore, be it

Resolved: That Article IV, Section 6.—Benevolence Fund—be deleted in its entirety (deletion in brackets) as follows:

[At least $1.00 out of the annual dues paid by each active member of the Association shall be allocated to the Physicians' Benevolence Fund, Inc., a Corporation, and shall be used for the purposes as set forth in that Corporation's Articles and Bylaws.]

ACTION: Tabled for one year; to be acted upon at the 1974 meeting of the House of Delegates.

* * *

ARTICLE III, PART A, SECTION 1(d)—VOTING PRIVILEGES FOR SCIENTIFIC BOARD REPRESENTATIVES IN THE HOUSE OF DELEGATES

Introduced by: Council

Constitutional Amendment 4-73
Committee G

Resolved: That Article III, Part A, Section 1 (d)—House of Delegates composition shall be amended by deleting the words in brackets and adding the words in italics, so that this Subsection shall now read:

"(d) Ex officio, [without] *with* the right to vote, [eighteen (18)] *twenty-one (21)* members of the Scientific Board selected as provided in the Bylaws, and . . ."

ACTION: Tabled for one year; to be acted upon at the 1974 meeting of the House of Delegates.

Visit the

Scientific and Organizational Exhibits

Garden Lane, California Room
and
North Lounge

MARCH 2-5, 1974
9:00 a.m. to 5:00 p.m.

Woman's Auxiliary

Forty-Fourth Annual Convention

MARCH 2 - 5, 1974

Headquarters: Hilton Hotel, San Francisco

Mrs. William R. Flood .... *Chairman*
Mrs. Bradford P. Cohn .... *Co-Chairman*

REGISTRATION—Tower Lobby

Saturday, March 2—12 noon to 4:00 p.m.
Sunday, March 3—9:00 a.m. to 4:00 p.m.
Monday, March 4—7:30 a.m. to 4:00 p.m.
Tuesday, March 5—7:30 a.m. to 10:00 a.m.

SATURDAY, March 2—Pre-Convention

1:00 p.m.	Presentation of Mrs. Thomas A. Gibson, Auxiliary President, to CMA House of Delegates, Hilton Plaza
4:00 p.m.	Executive Committee Meeting, President's Suite

SUNDAY, March 3

1:00 p.m.	Pre-Convention Board Meeting, Cypress Room
6:30 p.m.	Presidents' Reception

MONDAY, March 4

8:30 a.m.	Opening Session of House of Delegates, Pacific Room
11:30 a.m.	Presidents' Luncheon, Hilton Plaza
1:30 p.m.	Afternoon Session of House of Delegates, Pacific Room

TUESDAY, March 5

8:30 a.m.	Final Session of House of Delegates, Pacific Room
1:00 p.m.	Orientation Meeting, Ballrooms 7 and 8
1:30 p.m.	Presentation of Mrs. Harry S. Dvorsky, Incoming President, to the CMA House of Delegates, Hilton Plaza
4:00 p.m.	Post-Convention Board Meeting, Ballroom 9

HOSPITALITY CENTER—Tower Lobby

Sunday, March 3—9:00 a.m. to 4:00 p.m.
Monday, March 4—7:30 a.m. to 11:30 a.m.
Tuesday, March 5—7:30 a.m. to 11:30 a.m.

This is a tentative schedule of events for the 1974 WA-CMA Convention. County officers will receive more information through "Communique," but please note the dates now and plan to attend.

MRS. THOMAS A. GIBSON
President

MRS. HARRY S. DVORSKY
President-Elect

APPLICATION FOR HOTEL ACCOMMODATIONS

103rd Annual Session • MARCH 2-6, 1974

CALIFORNIA MEDICAL ASSOCIATION and WESTERN SCIENTIFIC ASSEMBLY

SAN FRANCISCO HILTON HOTEL • SAN FRANCISCO

Registration Opens Friday Afternoon, March 1

SCIENTIFIC SESSIONS
Begin Saturday Morning, March 2

HOUSE OF DELEGATES OPENING SESSION
Saturday Afternoon, March 2

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1. Fill in the form below **completely** for room accommodations at the CMA's 1974 Annual Session.
2. Your reservation request should include the definite date and hour of your arrival and departure.
3. All reservations, **except for suites,** must be made through the San Francisco Hilton Hotel, Mason at O'Farrell Street, San Francisco, Ca. 94102, **by February 2, 1974.**
4. **All SUITE reservations must be cleared through the CMA Convention Office, San Francisco.** If you are requesting a suite, direct your requests to: CMA Convention Office, 731 Market Street, San Francisco, Ca. 94103.
5. **Cancellations:** Please notify San Francisco Hilton Hotel, Mason at O'Farrell Street, San Francisco, Ca. 94102, of all cancellations.

   Changes: All other changes are also to be made directly with hotel at all times.

- -

SAN FRANCISCO HILTON HOTEL

	Main Building	Tower
Singles	$23-39	$33-48
Twins or doubles	$32-48	$42-57
Additional person in room	$ 9	$ 9
1 Bedroom suites	$74 & up	$95 & up

Send to: SAN FRANCISCO HILTON HOTEL RESERVATIONS
Mason at O'Farrell Street, San Francisco, Ca. 94102

Please reserve the following accommodations for the CMA's 1974 Annual Session in San Francisco, March 2-6, 1974:

Please Check Preference: ☐ MAIN BUILDING ☐ MAIN BUILDING FLOOR 5-11 ☐ TOWER
(INSIDE FREE PARKING AVAILABLE FLOORS 5-11 MAIN BUILDING)

Single Bedroom $______ Twin-Bedded $______ Double Bed $______ Suite $______

Arrival (date) ________ Hour ______ a.m. p.m. Departure (date) ________ Hour ______ a.m. p.m.

The name and address of each hotel guest must be listed. Include names and addresses of **each** person in a double or twin-bedded room, and names and addresses of **all other persons** for whom you are requesting reservations.

Your Name ________________________

Address ______________ County ____________

City and State ______________ Zip Code ________

GUESTS' NAMES AND ADDRESES:

Reports of officers, commissions and committees of the California Medical Association, together with the following audited financial statements for the fiscal year ended June 30, 1973, are printed in the *Annual Report Bulletin,* which is distributed to Delegates and Alternates before the meeting of the House of Delegates. The *Bulletin* is also available to any member of the Association on request directed to Robert L. Thomas, Executive Director, California Medical Association, 731 Market Street, San Francisco, California 94103.

Financial Reports

CALIFORNIA MEDICAL ASSOCIATION
and
TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION

Report of CERTIFIED PUBLIC ACCOUNTANTS

CALIFORNIA MEDICAL ASSOCIATION:

We have examined the balance sheets of California Medical Association and Trustees of the California Medical Association at June 30, 1973, and the related statement of income and expenses and statement of excess of assets over liabilities for the year then ended. Our examinations were made in accordance with generally accepted auditing standards, and accordingly included such tests of the accounting records and such other auditing procedures as we considered necessary in the circumstances.

In our opinion, the statements referred to above present fairly the financial positions of California Medical Association and Trustees of the California Medical Association at June 30, 1973, and the results of their operations for the year then ended, in conformity with generally accepted accounting principles applied on a basis consistent with that of the preceding year, after restatement of the financial statements for that year as described in Notes 1(d) and (b).

JOHN F. FORBES & COMPANY

San Francisco, California
August 24, 1973

CALIFORNIA MEDICAL ASSOCIATION
(A Nonprofit Association)

Balance Sheet, June 30, 1973 and 1972, and Comparison

ASSETS	1973	1972 (Restated—Note 1(d))	Increase *(Decrease)*
CASH:			
Commercial accounts	$ 76,732	$ 20,777	$ 55,955
Savings account	4,014	657,280	*(653,266)*
Total cash	80,746	678,057	*(597,311)*
CERTIFICATES OF DEPOSIT	1,798,852	750,000	1,048,852
ACCOUNTS RECEIVABLE, NET	135,893	108,510	27,383
ACCRUED INTEREST	6,357	6,000	357
NOTES RECEIVABLE:			
Central California Blood Bank	27,801	46,418	*(18,617)*
Other	..	800	*(800)*
Total notes receivable	27,801	47,218	*(19,417)*
PREPAID EXPENSES AND OTHER ASSETS:			
Retirement program premium (Note 1 (e))	33,521	29,267	4,254
Insurance	5,938	4,575	1,363
Deposits	13,366	7,777	5,589
Other	11,976	10,706	1,270
Total prepaid expenses and other assets	64,801	52,325	12,476
OFFICE FURNITURE AND EQUIPMENT (Notes 1, 2, and 3)	153,608	161,388	*(7,780)*
NOTE AND ACCOUNTS RECEIVABLE, AFFILIATED ORGANIZATIONS:			
Trustees of the California Medical Association:			
Demand note with interest at 4% per year	125,000	125,000	..
Account receivable	..	52,419	*(52,419)*
	125,000	177,419	*(52,419)*
Other—Accounts receivable:			
Six Ninety Three Sutter Publications, Inc.	45,016	4,291	40,725
California Medical Education and Research Foundation, Inc.	22,371	2,565	19,806
Miscellaneous	9,493	9,516	*(23)*
Total note and accounts receivable, affiliated organizations	201,880	193,791	8,089
	$2,469,938	$1,997,289	$ 472,649

LIABILITIES	1973	1972	Increase *(Decrease)*
ACCOUNTS PAYABLE:			
American Medical Association	$ 483,225	$ 48,857	$ 434,368
Other	58,009	36,779	21,230
Total accounts payable	541,234	85,636	455,598
DUE TO AFFILIATED ORGANIZATIONS:			
Trustees of the California Medical Association	1,573	..	1,573
Physicians' Benevolence Fund, Inc.	24,943	24,872	71
Total due to affiliated organizations	26,516	24,872	1,644
LONG-TERM DEBT—EQUIPMENT LEASE CONTRACT (Note 3)	114,189	121,445	*(7,256)*
DEFERRED INCOME—DUES AND SUBSCRIPTIONS APPLICABLE TO THE SUCCEEDING FISCAL YEAR (Note 1)	1,272,720	1,258,939	13,781
Total liabilities	1,954,659	1,490,892	463,767
EXCESS OF ASSETS OVER LIABILITIES (Note 4)	515,279	506,397	8,882
	$2,469,938	$1,997,289	$ 472,649

See notes to financial statements.

Statement of Excess of Assets Over Liabilities Years Ended June 30, 1973 and 1972, and Comparison

	1973	1972 (Restated— Note 1(d))	Increase *(Decrease)*
UNRESTRICTED:			
Balance, beginning of year	$299,604	$257,875	$ 41,729
Excess of income over expenses for the year	8,882	83,457	*(74,575)*
Transfer to restricted	4,441	41,728	*(37,287)*
	4,441	41,729	*(37,288)*
Balance, end of year	304,045	299,604	4,441
RESTRICTED AS TO USE (Note 4):			
Balance, beginning of year	206,793	165,065	41,728
Transfer from unrestricted	4,441	41,728	*(37,287)*
Balance, end of year	211,234	206,793	4,441
EXCESS OF ASSETS OVER LIABILITIES (Note 4)	$515,279	$506,397	$ 8,882

See notes to financial statements.

Statement of Income and Expenses Years Ended June 30, 1973 and 1972, and Comparison

	1973	Percent of Total Income	1972 (Restated— Note 1(d))	Percent of Total Income	Increase *(Decrease)*
INCOME:					
Membership dues, less portion allocated to subscriptions to "California Medicine" (Note 1)	$2,467,823	93.8%	$2,424,523	95.0%	$ 43,300
Less collection fees allowed county societies	19,076	0.7	22,014	0.8	*(2,938)*
Net membership dues	2,448,747	93.1	2,402,509	94.2	46,238
Booth rentals at annual session	43,128	1.6	41,989	1.6	1,139
Fees, postgraduate courses	17,595	0.7	20,310	0.8	*(2,715)*
Fee for collection of American Medical Association dues	25,597	1.0	25,375	1.0	222
Interest earned	91,524	3.5	62,591	2.4	28,933
Other	3,365	0.1	105	..	3,260
Total income	2,629,956	100.0	2,552,879	100.0	77,077
EXPENSES:					
Physicians' Services and Programs	362,176	13.8	369,774	14.5	*(7,598)*
Divisional Programs	1,652,829	62.8	1,573,741	61.6	79,088
General expenses	527,949	20.1	502,896	19.7	25,053
	2,542,954	96.7	2,446,411	95.8	96,543
Contributions	24,608	0.9	37,312	1.5	*(12,704)*
Excess of expenses over income "California Medicine"	27,927	1.1	24,504	0.9	3,423
Total	2,595,489	98.7	2,508,227	98.2	87,262
EXCESS OF INCOME OVER EXPENSES BEFORE TRANSFER FROM TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION	34,467	1.3	44,652	1.8	*(10,185)*
EXCESS OF INCOME OVER EXPENSES (EXPENSES OVER INCOME) OF TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION	*(25,585)*	*(1.0)*	38,805	1.5	*(64,390)*
EXCESS OF INCOME OVER EXPENSES	$ 8,882	0.3%	$ 83,457	3.3%	$*(74,575)*

See notes to financial statements.

Notes to Financial Statements

NOTE:

1. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

(a) Membership Dues

Dues are assessed on a calendar year basis. At the beginning of each calendar year, based upon estimated membership for the year, the Association records dues receivable from members and credits deferred income. The deferred income is taken into income at an even rate throughout the year. Any excess or deficit of dues in comparison with the estimated amount is taken directly into income.

(b) Subscriptions

Member subscriptions to "California Medicine" are recorded on the same basis as membership dues. Nonmember subscriptions are taken into income at an even rate throughout the 12-month period following the month of receipt.

(c) Office Furniture and Equipment

Acquisitions prior to July 1, 1966 are carried at a nominal amount of $1. At May 13, 1966, a firm of appraisers estimated that the sound value of assets then owned was $104,415.

Assets acquired after July 1, 1966, are carried at cost. Depreciation is based on the estimated useful lives of the assets (5 to 10 years) and the straight line method.

When assets are retired or otherwise disposed of, the related cost and accumulated depreciation are removed from the respective accounts and the net difference, less any amount realized from disposition, is reflected in income. Maintenance and repairs are generally charged to income. Major expenditures for renewals and betterments are capitalized and depreciated over the estimated useful lives of the related assets. (See Note 2.)

(d) Assets Held in Trust

The Trustees of the California Medical Association hold in trust a large portion of the assets utilized by the California Medical Association. These assets are not included in the financial statements of the Association. (See Note 4.)

In accordance with Section 501(c)(2) of the Internal Revenue Code the excess of income over expenses (expenses over income) realized from these assets is transferred to the Association each year. During the year, Trustees adopted the equity method of accounting for investments in common stock of unconsolidated subsidiaries and restated the financial statements of the prior year to reflect this change. The Association's financial statements have also been restated to reflect the effect of the restatement of the financial statements of Trustees.

(e) Retirement Program

In addition to the Group Pension Program which became effective on January 1, 1961, the California Medical Association has arranged for the funding of a Past Service Pension Plan for certain full-time employees. This resulted in an additional liability of $62,734 which is being amortized over 20 years from January 1, 1966. The Travelers' Insurance Company has underwritten the plan and will furnish annuity contracts as eligible employees retire. Because the current service benefits and all of the benefits for retired employees have already been purchased under the contract, there is a liability only for the unfunded value of vested benefits. This liability amounted to $51,117 on January 1, 1973. It is neither recorded on the books of the Association nor included in the accompanying balance sheet.

The pension expense for the year was $61,945. This expense is determined by the underwriter each year and may vary, depending on new qualifying employees and credits arising from qualified employees leaving the Association.

2. OFFICE FURNITURE AND EQUIPMENT

Assets acquired after July 1, 1966, are summarized as follows:

	Cost	Depreciation or Amortization
Office furniture and equipment:		
Balance, July 1, 1972	$215,600	$54,212
Purchased during the current year	15,978	..
Provision for the current year	..	23,758
Sales, trade-ins, and retirements	*(1,175)*	*(1,175)*
Balance, June 30, 1973	$230,403	$76,795
Net book value	$153,608	

3. LONG-TERM DEBT

Certain equipment for which the Association has entered into a lease is accounted for as purchased equipment. The cost of this equipment, $122,580, is included in office furniture and equipment, less applicable depreciation. The lease provides for payments of $1,675 monthly for 120 months to April 26, 1982. The lease liability at June 30, 1973, $114,189, is stated at the discounted present value of the remaining obligation. The lease provides options at the expiration date to renew the lease indefinitely at 1/12 of the present annual rental, to purchase the equipment at 10% of the original cost, to return the equipment to the lessor, or to return the equipment to the lessor as a trade-in on new equipment to be leased. (See Note 2.)

4. COMBINED NET WORTH

The Trustees of the California Medical Association is a wholly-owned subsidiary of the California Medical Association. The Trustees hold in trust a large portion of the assets utilized by the California Medical Association. The combined net worth of the two organizations is summarized as follows:

Entity	1973	1972	Increase
California Medical Association:			
Restricted as to use	$ 304,045	$ 299,604	$4,441
Unrestricted	211,234	206,793	4,441
	515,279	506,397	8,882
Trustees of the California Medical Association	1,511,371	1,511,371	..
	$2,026,650	$2,017,768	$8,882

The combined net worth at June 30, 1973 shown in the summary above does not include the excess of the appraised value of furniture and office equipment acquired prior to July 1, 1966 over accumulated depreciation and nominal carrying value, approximately $31,300.

5. COMMITMENTS

The Association rents its San Francisco office facilities from Trustees of the California Medical Association for approximately $71,000 per annum. (See Note 6.) The annual rentals for office facilities in Sacramento and Los Angeles are $20,940 through 1978, and $3,180 through 1975, respectively. In addition, certain equipment is leased at approximate annual rentals which for the years ended June 30 are as follows: 1974—$12,400; 1975—$9,200; 1976—$5,500; 1977—$2,200.

6. SUBSEQUENT EVENTS

In July 1973, Trustees of the California Medical Association entered into agreements to sell its properties which the Association rents for office facilities. The Association subsequently entered into a lease agreement for other office space. This lease shall commence on November 15, 1973, or December 1, 1973, and shall continue for the term of 10 years at an annual rental of $182,857.20. At the option of the California Medical Association this lease may be terminated at the fifth anniversary of taking possession by paying $3.00 per square foot of space, approximately $100,000.

TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION

(A Nonprofit Corporation)

Balance Sheet, June 30, 1973 and 1972, and Comparison

ASSETS	1973	1972 (Restated—Note 1)	Increase *(Decrease)*
CASH:			
Commercial account	$ 3,282	$ 1,288	$ 1,994
Savings accounts	61,249	139,711	*(78,462)*
Total cash	64,531	140,999	*(76,468)*
INVESTMENTS IN MARKETABLE SECURITIES, AT COST (Note 1):			
U.S. Treasury bills, maturing by November 20, 1973 (market value $168,147)	168,147	..	168,147
U.S. Treasury bond	..	100,000	*(100,000)*
Corporate fixed income securities (market value, 1973, $304,313; 1972. $311,062)	301,719	301,719	..
Listed common stocks (market value, 1973, $493,151; 1972, $663,351)	506,659	663,586	*(156,927)*
Total investments in marketable securities	976,525	1,065,305	*(88,780)*
RECEIVABLE FROM CALIFORNIA MEDICAL ASSOCIATION	1,573	..	1,573
INVESTMENTS IN WHOLLY-OWNED SUBSIDIARIES (Note 1):			
Pacific Magnetic Tape Equipment Co.	107,491	92,327	15,164
Six Ninety Three Sutter Publications, Inc.	31,996	23,127	8,869
Total investments in wholly-owned subsidiaries	139,487	115,454	24,033
ACCRUED INTEREST AND DIVIDENDS	10,176	6,321	3,855
PROPERTIES, AT COST (Notes 1, 2, and 4):			
Buildings and improvements	420,282	413,578	6,704
Carpets, installation, and other	21,029	21,029	..
	441,311	434,607	6,704
Less accumulated depreciation	151,384	147,423	3,961
	289,927	287,184	2,743
Land	180,217	180,217	..
Properties, net	470,144	467,401	2,743
EQUIPMENT, AT NOMINAL VALUE	1	1	..
CASH SURRENDER VALUE OF LIFE INSURANCE (Note 3)	86,932	78,242	8,690
ACCRUED REAL ESTATE TAXES (contra)	25,000	25,000	..
PREPAID INSURANCE AND OTHER EXPENSES	4,142	2,231	1,911
	$1,778,511	$1,900,954	$*(122,443)*

LIABILITIES

	1973	1972 (Restated—Note 1)	Increase *(Decrease)*
ACCOUNTS PAYABLE AND ACCRUED EXPENSES:			
Audio-Digest Foundation	$ ..	$ 5,646	$ *(5,646)*
California Medical Association	..	52,419	*(52,419)*
Interest and accrued expenses	5,918	874	5,044
Total accounts payable and accrued expenses	5,918	58,939	*(53,021)*
ACCRUED REAL ESTATE TAXES PAYABLE (contra)	25,000	25,000	..
NOTES PAYABLE:			
California Medical Association, payable on demand, with interest at 4% per year—Unsecured	125,000	125,000	..
The Connecticut Mutual Life Insurance Company, with deed of trust as collateral (payable in quarterly installments of $2,506, including interest at 4¼% per year, to December 1, 1973)	..	4,450	*(4,450)*
Total notes payable	125,000	129,450	*(4,450)*
TRUST FUNDS (Note 3)	109,287	174,804	*(65,517)*
DEFERRED INCOME	1,935	1,390	545
EXCESS OF ASSETS OVER LIABILITIES:			
Balance, beginning of year	1,511,371	1,511,371	..
Excess of income over expenses (expenses over income) for the year before transfer to California Medical Association	*(25,585)*	38,805	*(64,390)*
Transfer to California Medical Association	25,585	*(38,805)*	64,390
Balance, end of year	1,511,371	1,511,371	..
	$1,778,511	$1,900,954	$*(122,443)*

See notes to financial statements.

TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION

Statement of Income and Expenses Years Ended June 30, 1973 and 1972, and Comparison

	1973	1972 (Restated— Note 1(d))	Increase *(Decrease)*
INCOME:			
Net income from rental properties	$ 7,145	$ 15,168	$*(8,023)*
Interest	33,223	35,181	*(1,958)*
Dividends—Listed common stocks	18,074	18,471	*(397)*
(Loss) on sale of investments (Note 1)	*(76,613)*	*(13,034)*	*(63,579)*
Equity in net income of wholly-owned subsidiaries (Note 1):			
Pacific Magnetic Tape Equipment Co.	21,464	17,946	3,518
Six Ninety Three Sutter Publications, Inc.	8,869	1,201	7,668
	12,162	74,933	*(62,771)*
EXPENSES (OTHER THAN PROPERTY)— PROFESSIONAL FEES, INSURANCE, AND MANAGEMENT	32,066	30,162	1,904
	(19,904)	44,771	*(64,675)*
OTHER CHARGES—PROVISION FOR RETIREMENT OR OTHER BENEFITS FOR:			
Robert L. Thomas	2,741	2,802	*(61)*
Howard Hassard	2,940	3,164	*(224)*
	5,681	5,966	*(285)*
EXCESS OF INCOME OVER EXPENSES (EXPENSES OVER INCOME) BEFORE TRANSFER TO CALIFORNIA MEDICAL ASSOCIATION	*(25,585)*	38,805	*(64,390)*
TRANSFER TO CALIFORNIA MEDICAL ASSOCIATION	$25,585	$*(38,805)*	$64,390

See notes to financial statements.

Notes to Financial Statements

NOTE:

1. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

(a) Investments in Marketable Securities

Marketable securities are carried at cost. Gain or loss on sale of investments is determined on the basis of identified cost. Market value is determined by the closing price as listed on the New York Stock Exchange. Dividend income is recorded on the ex-dividend date.

(b) Investments in Wholly-owned Subsidiaries

Trustees own all of the outstanding capital stock of Six Ninety Three Sutter Publications, Inc. and Pacific Magnetic Tape Equipment Co. In prior years, these investments were carried at their costs of $1,000 and $9,000, respectively. During the year ended June 30, 1973, the accounting for these investments was changed to the equity method in accordance with Opinion 18 of the Accounting Principles Board of the American Institute of Certified Public Accountants. Accordingly, these investments are carried at the amount of stockholder's equity shown in the balance sheets of the respective subsidiaries and their net income is reflected in the income statement of Trustees. The financial statements of Trustees for the previous year have been restated on the equity method as described above.

(c) Properties

Properties are stated at cost. The 679 Sutter Street building and improvements are being depreciated over 20 years and carpets, installation, and other property over 10 years. The straight line method is used.

Management decided in 1971 to discontinue recording depreciation on the 693 Sutter Street Building, which is used almost entirely by the California Medical Association. Proper maintenance is expected to keep the building in good condition.

When properties are retired or otherwise disposed of, the related cost and accumulated depreciation are removed from the respective accounts and the net difference, less any amount realized from disposition, is reflected in income. Maintenance and repairs are generally charged to income. Major expenditures for renewals and betterments are capitalized and depreciated over the estimated useful lives of the related assets.

2. PROPERTIES

The properties held by Trustees of the California Medical Association are summarized as follows (see Note 4):

	693 Sutter Street	679 Sutter Street	Total
Buildings and improvements	$338,964	$ 81,318	$420,282
Carpets, installation, and other	20,359	670	21,029
	359,323	81,988	441,311
Less accumulated depreciation	124,953	26,431	151,384
	234,370	55,557	289,927
Land	87,400	92,817	180,217
	$321,770	$148,374	$470,144

3. TRUST FUNDS

These funds are summarized as follows:

Morris Herzstein Bequest (accumulated earnings remitted to Trustees of the California Medical Association)		$ 2,388
Life insurance retirement plan for:		
Howard Hassard		73,747
Robert L. Thomas		13,185
Other:		
Howard Hassard—Deferred compensation	$13,000	
Murray Klutch—Funded by payroll deductions	6,967	19,967
		$109,287

The Wells Fargo Bank is the trustee under the Morris Herzstein trust. The corpus is invested in 4,480 units of Wells Fargo Bank Common Stock Fund with a value of $24,237 at June 30, 1973.

The life insurance retirement plan for legal counsel is offset by the cash surrender value of a life insurance policy.

4. SUBSEQUENT EVENTS

In July 1973, Trustees entered into agreements to sell its properties at 693 Sutter Street and 679 Sutter Street for $375,000 and $175,000, respectively.